THE 1947 YEAR BOOK *of* GENERAL MEDICINE

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Departments *of the* Year Book *of* General Medicine

Infectious Diseases

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INFECTIOUS DISEASES

GEORGE F DICK M D

PART I

INFECTIOUS DISEASES

GENERAL CONSIDERATIONS

Distribution of Morbidity of Epidemic Diseases with Regard to Age is discussed by Helge Petersen[1] (Copenhagen) Since newborn infants possess a high degree of immunity to infectious diseases (inborn immunity) and infectious diseases often impart immunity (acquired immunity) morbidity is low at the earliest age when most persons still possess their inborn immunity and during advanced age when most persons have acquired immunity It follows that there must be an intermediate age *range in which morbidity is greatest (period of children s diseases)* The age distribution resulting from the two aforementioned facts can be computed on the basis of the law governing disappearance of the inborn immunity with age incidence of infection and density of the population Comparisons were made between the theoretical results and the actual age distribution for various infectious diseases For example it was established that the differences between morbidity rates during the great polio myelitis epidemics in Sweden in 1911–13 agreed fairly well with the theoretical computation

The law applied to the disappearance of inborn immunity is based on the assumption that for every time unit the same fraction of existing immune individuals will lose immunity which means that the existing number of individuals with inborn immunity will decrease according to an exponential law This agrees only roughly with the few observations available These show a decrease in inborn immunity which immediately after birth is slower than that calculated according to the exponential law but the agreement increases with the time elapsed since

(1) A ta m d S d ૅ (pp 179) 1 5 1 61 1946

Hosp New York City) state that the human placenta readily transmits diffusible substances such as antitoxins and antibodies and that lack of immunity in the mother is reflected in the baby Apparently as a result of childhood prophylaxis about 50 per cent of women today lack immunity to diphtheria in contrast to 85 per cent immunity in the preimmunization era of the past generation The authors recently showed that about 80 per cent of women and about 85 per cent of babies are not immune to whooping cough Since the infant does not produce a proper titer of antibodies by active immunization it should be protected during the first few months of life by passive immunization Passive immunity for this period can be conferred against diphtheria whooping cough and probably other diseases for which there are effective vaccines by active immunization of the mother in the last trimester of pregnancy

Vaccine and toxoid therapy during pregnancy may serve to suppress formation of anti Rh antibodies This method of counterimmunization offers an additional reason for active immunization in pregnancy but for this purpose inoculations should be given from the first trimester through the last

Active maternal immunization has no observable deleterious effects on the offspring but the mother often has local discomfort for a brief period and at times fever and systemic reactions develop which however have no ill effects on the pregnancy The following program is recommended An intradermal test with a 1 10 dilution of diphtheria toxoid is first performed on all Schick positive patients If the reaction is definitely positive within 30 minutes either diphtheria toxoid is omitted (in case the reaction is very marked) and plain pertussis vaccine given or the initial dose of 0 1 cc diphtheria toxoid is followed by 0 25 0 5 and 1 cc added to the pertussis vaccine in the same syringe The authors favor use of a fluid diphtheria toxoid combined with a pertussis vaccine containing 15 billion bacilli per cc beginning with 1 cc followed by 2 cc. for two doses and then 3 cc totaling

birth As the inborn immunity disappears rapidly during the first year of life the discrepancy at an early age does not as a whole affect the age distribution of morbidity However regarding diseases in which the inborn immunity is lost comparatively late e g in pulmonary tuberculosis there is a significant discrepancy between the theoretically computed and the actual course of variation of morbidity with age particularly in young subjects The duration of inborn immunity is therefore considered as a property possessed by all individuals but to a varying degree so that the individual values for the duration of inborn immunity are distributed around the average duration for all individuals according to the gaussian law of distribution A comparison with the only observation available showed perfect agreement Accordingly the phenomenon of inborn immunity can be described in its variation in the time factor by an average duration which is the one most frequently occurring and by a dispersion which gives the frequency of deviating values of duration The average duration and the dispersion of inborn immunity to pulmonary tuberculosis can thus be determined and a new curve computed for the variation of morbidity with age. This curve was found to agree with the actual one

The theory advanced in this study permits a computation of how the number of individuals who have had the disease varies with age Records are not available for most diseases but they do exist for pulmonary tuberculosis in that persons who react to tuberculin may be assumed to be identical with those who have contracted tuberculosis A comparison between the actual figures and theoretical computations shows good agreement provided no foreign sources of infection are present The theory also makes it possible to compute on the basis of the actual curve of age distribution of morbidity the extent of a possibly existing latent infection i e an infection which leaves immunity without producing manifestations of the disease

Effects of Active Immunization of Mother on Offspring Philip Cohen and Samuel J Scadron[2] (Beth Israel

(2) J Pediat. 29 609-619 November 1946

embryo Material is stained and examined microscopically If no organisms are found the coverglass may be replaced and the egg reincubated and examined again 24–48 hours after inoculation

Chemical Studies on Host Virus Interactions Effect of Bacteriophage Adsorption on Multiplication of Its Host Escherichia Coli B Some Data on Composition of Bacteriophage T2 Seymour S Cohen and Thomas F Anderson[4] (Philadelphia) observed that addition of active or irradiated T2 and T4 bacteriophages to Esch coli B stops bacterial multiplication The respiratory rate and quotient of the inhibited bacteria remained at the values observed just before infection A respiratory rate decrease which occasionally appears can be roughly correlated with change of turbidity of the suspension An intracellular inhibitor of multiplication appears to be liberated into lysates A similar substance has been separated from normal Esch coli B after sonic disintegration These bacteriostatic preparations contain cytoplasmic granules with lactic acid dehydrogenase activity

The relationships between inhibition of multiplication by phage and that produced by the intracellular substance liberated by lysis are not clear The initial lysis of a few organisms in a concentrated suspension might possibly liberate enough intracellular inhibitor to add an additional interference effect to that induced by the phage alone This might then be responsible for the aberrancies in one step growth curves determined in concentrated bacterial suspensions

Virus Hemagglutination With the possible exception of the bacteriophage group of viruses the nature of factors responsible for virus specificity is not known In this group the virus unites with a specific component on the cell in some cases an antigenic surface polysaccharide Virus specificity may be explainable in terms of chemical or metabolic relations between virus and cell In an attempt to clarify this problem Max Bovarnick and Patrick M de Burgh[5] (Harvard Univ) studied factors respons

(4) J E p r M d. 84 511 5 3 N mbe 1946
(5) Science 105 550 55 M y 23 1947

120 billion pertussis bacilli In sensitive subjects the diphtheria toxoid in increased dosage is added to pertussis vaccine as described This method causes fewer and less severe reactions than alum preparations which in addition often leave annoying nodules When the infant is 6 months old appropriate active immunization should be carried out

Clinical Applications of Chick Embryo Cultures Adaptation for Use by General Practitioner in Bacteriologic Diagnosis of Clinical Problems is described by Henry K Silver and C Henry Kempe[3] (Univ of California) *Easy obtainability in rural* areas of fertile hens eggs provides the general practitioner with a sensitive culture medium in a suitable sterile container ready for immediate use Causative organisms of such diseases as otitis media purulent skin infections and empyema may readily be identified in this medium which also may be used for culture of spinal fluid in suspected meningitis as well as for culture of material from operative sites

METHOD —A hen s egg incubated for 5–10 days is candled to determine viability of the embryo The viable embryo is seen as a dark spot with a radiating network of blood vessels when the egg is held at the open end of a cardboard cone placed over a flashlight The areas on the shell overlying the embryo and the air sac (which usually lies at the rounded end of the egg) are marked with a pencil and over the embryo area a circle of petrolatum is made The well formed by the petrolatum circle should be approximately ¼–⅜ in high and ½ in in diameter Several drops of half strength nitric acid solution is placed in the well and a drop at the air sac end of the egg and washed off with sterile water four to five minutes later A needle or probe is inserted through the thinned shell over the air sac and then the softened shell with the petrolatum ring is lifted off gently without injuring the shell membrane directly underneath A drop of sterile water is placed on this membrane and a slit made in it with scalpel or sterile needle and the shell membrane removed

Up to 2 5 cc fluid to be examined can now be dropped directly through the window The egg is resealed by covering the window with a sterile coverglass and then incubated at 98 6–103 F for five to eight hours The coverglass is then lifted off and a sterile wire loop touched to the moist surface of the

(3) J A M A 132 3 7 Oct 19 1946

virus Virus coated cells subjected to the action of the immune hemolytic system present certain differences from uncoated cells which appear to depend on the concentra tion of allantoic fluid It is possible that the coating of the erythrocytes by antivirus serum may be an im portant factor in aiding the host to resist virus infections As host resistance in several virus diseases including in fluenza *cannot be correlated with demonstrable neutraliz* ing antibodies in the serum it may be that resistance is partially determined by presence or absence of antibody coated cells Future investigations to explain the action of these cells in resisting invasion by viruses might con tribute to the understanding of the mechanism of im munity to virus diseases

The experiments in which erythrocytes refractory to influenza virus were subjected to the action of vaccinia virus strongly suggest that red blood cells have different receptors for the two viruses Elution of influenza virus from the red cells evidently alters or destroys the influenza virus receptors but does not affect the vaccinia virus receptors It is impossible to compare the different re ceptors because none has been isolated However it may be presumed that tissue cells have different receptors for different viruses and that the state of the receptors may determine whether or not actual invasion and parasitism of the cells by the virus will take place

Knowledge of Human Virus Infections of Animal Origin K F Meyer and B Eddie[7] (Univ of California) summarize present knowledge of rabies psittacosis and arthropod borne encephalitides

Though the usual mode of transmission of rabies is by means of a bite several authentic cases are recorded of rabies which developed after hands had been licked by an infected animal In no case has it been proved that rabies followed ingestion of milk from a rabid cow or other animal

In an afflicted community every biting dog or cat must be suspected of having rabies Each ensuing wound must

(7) J A M A 133 8 828 M 2 1947

ible for the hemagglutination phenomena with respect to alteration of cell receptors by virus action

From red blood cells specifically agglutinated by certain viruses lipid extracts have been prepared which inhibit the hemagglutinating action of the same viruses for these cells This effect probably results from competitive combination of the extract with the virus Inhibition reactions thus far tested seem to demonstrate specificity corresponding to that shown by the viruses in these hemagglutinating actions Thus it is known that influenza virus agglutinates human and chicken red blood cells but not sheep cells whereas mumps virus agglutinates all three types of cells As was predicted human inhibitor was found to prevent the hemagglutinating action of influenza on both human and chicken red cells whereas sheep inhibitor had no effect on influenza virus Both human and sheep inhibitors interfered with action of mumps virus on human and chicken cells and to a lesser extent on sheep cells Prolonged contact of virus and inhibitor at 25 or 37 C resulted in inactivation of the inhibitor This evidence supports the hypothesis that the inhibitor is identical with or a derivative of the cell receptor

Hemagglutination Induced by Viruses Bernard A Brody Ir [6] observed increased production of influenza virus in the developing chick embryo when a Chamberland L_5 filtrate of an influenza infected allantoic fluid was used as the inoculum On the basis of several hundred tests with chicken red blood cells subjected to vaccinia virus he developed the hypothesis that no sample of chicken red cells adult or embryonic is completely resistant to vaccinia virus induced hemagglutination Cells rendered refractory to influenza virus were shown to be susceptible to vaccinia virus induced hemagglutination

The results obtained with regard to serum inhibition of virus induced hemagglutination suggest that the reaction may be blocked when the serum combines with the virus or when it coats the receptors of the cell for the

(6) Y le J Biol & Med. 19:29 61 Octobe 1946

during the acute phase and (2) demonstration of a significant rise in titer in complement fixing antibodies A two to fourfold increase in titer together with objective signs of a pulmonary involvement warrants tentative diagnosis of psittacosis and prompt therapy

Present observations suggest that when the psittacosis virus is inside the cells it is protected against penicillin and that only in the extracellular phase when it is not actually multiplying is it susceptible to antibiotics This necessitates large doses administered in rapid succession early in the course to cut the number of virus elements to a low level and permit the normal defense mechanism of the body to dispose of the remainder

Recent demonstration of the existence of the virus of both western equine encephalomyelitis and St Louis encephalitis in the Culex tarsalis mosquito of endemic territories explains the prevalence of these infections during hot weather in areas subject to agricultural irrigation and periodic flooding of streams Morbidity due to western and eastern equine virus is highest in children under five Fatality rates for both infections vary between 3 and 22 per cent For adequate diagnosis two serum specimens must be examined for any significant rise in antibody titer which may take place during the time between onset of the acute phase and end of the convalescent period

Vector control constitutes the most effective weapon available against rabies psittacosis and the arthropod borne encephalitides

Virus Disease from the Clinical Point of View Conrad Wesselhoeft[8] (Harvard Univ) points out that viruses multiply only in living susceptible cells and generally show a selective affinity for certain cells The viruses of rabies and poliomyelitis multiply only in cells of the nervous system the virus of mumps multiplies in glandular tissues as well as in cells of the nervous system the yellow fever virus may be found in the blood during the height of the disease the influenza virus multiplies in the epithelial

(8) M Cl N th Am 30 1029 10 3 September 1946

be thoroughly cleansed with soap and water and if the animal is thought to be rabid local treatment must be carried out to inactivate any virus deposited with the saliva Deep puncture wounds should be surgically exposed and irrigated with 20 per cent solution of medicinal soft soap Nitric acid is an accepted cautery but must not be used on face lacerations The animal should be taken alive and observed for two to three weeks Since local treatment cannot be depended on the physician will generally decide to administer postinfection vaccination as a safeguard The cause of paralysis following Pasteur treatment is not known but the number of paralytic accidents has greatly diminished since introduction of the Semple vaccine

Preinfection antirabies vaccination of dogs when combined with other dog control provisions appears to be the most satisfactory method of assuring prompt recession of rabies To promote co operation of the public vaccination should be performed free

The host range of psittacosis is now known to be much more extensive than was previously thought Contact with birds of the parrot or pigeon family is no longer essential to suspicion of the disease Inhalation of dessicated bird droppings constitutes the principal mode of transmission from birds to man There is evidence however that a patient fatally ill with psittacosis contracted from an avian source will eliminate virus in large amounts and could initiate human to-human transfer Hence every patient with severe pneumonitis should be isolated and not examined or treated without proper protection

Among 228 cases of psittacosis diagnosed at the laboratories of the Hooper Foundation in the last five years there was a mortality rate of 9 3 per cent In 219 case infections were definitely linked with exposure to birds including pigeons ducks canaries chickens grouse and parakeets and parrots Among 111 cases with ages listed there were no children aged 1–9 but 15 patients aged 10–19 Two criteria must be met in diagnosis of psittacosis (1) isolation of the virus from blood or sputum

during the acute phase and (2) demonstration of a significant rise in titer in complement fixing antibodies A two to fourfold increase in titer together with objective signs of a pulmonary involvement warrants tentative diagnosis of psittacosis and prompt therapy

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(8) M Cl N rth Am 30 1009 10 3 S pt mbe 1946

cells of the upper and lower respiratory tract and is never found in the blood

Certain virus diseases—chickenpox smallpox vaccinia measles mumps lymphogranuloma venereum infectious hepatitis atypical pneumonia and infectious mononucleosis—may produce transient false positive Hinton reactions for syphilis

Some viruses undergo mutation through environmental factors and resulting attenuated forms are the basis of vaccines Vaccines against smallpox rabies and yellow fever are established but are not without danger and certain precautions should be observed in their use Smallpox vaccination at the first birthday is safer than when the child enters school because postvaccinal encephalomyelitis though rare is even less frequent at the earlier age Generalized vaccinia is most apt to occur in the presence of a generalized eruption such as chronic eczema Therefore persons with generalized eczema should not be vaccinated and should be isolated from others recently vaccinated Because of the possibility of post rabies vaccination encephalomyelitis Pasteur treatment should not be given to a person bitten by a dog that is still living 14 days from the time of biting

Natural immunity to virus disease in some persons may be transient e g relative immunity to measles in the first two to four months of life Immunity may be acquired by subminimal infection by unrecognized attacks by well recognized attacks or by vaccination with attenuated viruses which induce a mild attack In some virus diseases such as smallpox vaccinia chickenpox measles and yellow fever acquired immunity is permanent whereas in others such as those of the upper respiratory tract immunity is temporary Immunity is presumed to depend on the virus remaining somewhere in the host in a state of latent inactivity in which it does not damage the cell but stimulates antibody formation in the surroundings by catalysis

Virus diseases spread by many methods Chickenpox measles mumps and upper respiratory tract infections

may be air borne from the respiratory passage of the donor to the recipient These are highly infectious in the prodromal period Contact infection by hand is also important A mask worn to prevent air borne infection is of little value if the wearer constantly handles the mask and then the patient Animals and insects transmit many virus diseases

Elementary or nuclear inclusion bodies are found in the lesions of virus infections These represent viruses in the cell and vary in number and character Round cell or giant cell infiltration endothelial cell proliferation and perivascular infiltration are also characteristic of virus pathology

Lymphocytic choriomeningitis is characterized by a fever on the sixth day after which the patient is well for a week Chill fever headache and signs of meningeal irritation due to involvement of the choroid plexus then develop Spinal fluid cell count varies from 50 to 1 000 cells with 90–100 per cent lymphocytes Symptoms subside after a week

The viruses of vaccinia measles chickenpox and mumps may cause an encephalitis which varies greatly in severity and is not proportionate to the severity of the original disease Encephalitis as evidenced by headache fever and rigidity of neck and spine occurs in about 10 per cent of patients of military age who have mumps It may precede accompany or follow the parotitis or may occur with signs of salivary gland involvement The last named form is differentiated from poliomyelitis by the subsequent rise in mumps antibody

Herpes simplex usually appears on the lips occasionally on the skin and rarely on the cornea or genitalia Frequently the primary infection occurs in childhood as aphthous stomatitis and persists through life generally remaining quiescent until activated by appropriate stimuli such as irritation from wind or sun a cold or a febrile infection

An etiologic relation between chickenpox and herpes zoster has been generally accepted in spite of the fact

that neither of the c diseases offers clinical immunity to the other

German measles when contracted early in pregnancy before formation of the placenta may result in congenital cataracts congenital heart defect and malformation of the mouth In the second month of pregnancy miscarriage *may occur but 90 per cent of fetuses which continue to* term show serious defects Prompt emptying of the uterus allows pregnancy to be undertaken again under more auspicious circumstances

No specific treatment is available for virus diseases once the incubation period is passed It is doubtful that convalescent serums are effective after the virus is established in the cells Treatment must be symptomatic

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ARTHRITIS

Rheumatoid Arthritis Hemolytic Streptococcus Precipitin Reactions Agglutination of Hemolytic Streptococci Because recent observations have cast doubt on supposedly specific reactions in which rheumatoid arthritis serum takes part Allan D Wallis[9] (Univ of Pennsylvania) has re examined precipitin and agglutinin reactions of this serum with extracts of streptococci groups A through G

It may be inferred from the results that *rheumatoid arthritis serums do not precipitate with crude extracts of* hemolytic streptococci groups B through F provided the saline control reaction is frankly negative When precipitation with saline occurs the precipitate with bacterial extracts is likely to be even stronger than with saline This suggests that precipitation of arthritis serum by saline may be enhanced by nonspecific adsorption of a heterologous antigen and the reaction mistaken for a genuine antigen antibody reaction Because of this enhancement a serum might appear *negative in the saline*

(9) Am J M S 213 87 96 Janua y 194

control tube and weakly positive in the presence of heterologous antigen

Of persons who have neither rheumatoid arthritis nor a recent hemolytic streptococcus infection about a fourth may have serum precipitins for selected strains of group A hemolytic streptococcus However both incidence and intensity of precipitates are greater with arthritis serums Similar results are obtained with group G streptococcus

With purified C substance the group specific carbohydrate of group A hemolytic streptococcus the discrepancy between arthritis and nonarthritis serums is greater precipitates with nonarthritis serums occurring much less frequently However positive reactions with arthritis serums are usually accompanied by positive saline control reactions

The normal nasopharynx contains a predominance of group A hemolytic streptococci The ability of rheumatoid arthritis serum to precipitate crude extracts of group A strains appears to be due to an enhancement of the action of antibodies normally present Both this enhancement and nonspecific antigen adsorption may be active in precipitation of arthritis serum with the C carbohydrate of group A streptococcus when normal precipitins are feeble

The author believes it unlikely that serums of patients with rheumatoid arthritis contain a genuine excess of hemolytic streptococcus precipitins

The ability of serums of patients with rheumatoid arthritis of more than one year s duration to agglutinate selected strains of group A hemolytic streptococci is known Wallis suggests that the potency of rheumatoid arthritis serums in agglutinating hemolytic streptococci may be related to the nonspecific serologic enhancing property which enables rheumatoid arthritis serum to exaggerate the action of normally present precipitins for streptococcus

The key to the explanation lies in previous observations that arthritis serums with high agglutinin titers can agglutinate suspensions of fine collodion particles even though

the particles have not been sensitized by exposure to antigen Wallis believes that ability of arthritis serums to agglutinate hemolytic streptococci of group A depends on how long and how recently the patient has harbored group A streptococci ability to agglutinate collodion depends chiefly on severity and duration of arthritis Either property could exist without the other but when both are present either will enhance the action of the other The enhancing effect of collodion agglutinin on streptococcus agglutinin is stronger than the reverse because the enhancements are apparently nonspecific and the fraction responsible for collodion agglutination appears quantitatively to exceed the streptococcus agglutinins

Wallis concludes that the tendency of serum from patients with rheumatoid arthritis to agglutinate hemolytic streptococci is due to a nonspecific enhancement of normally present agglutinins

[This work would not indicate that there was any specific causal role of streptococci in arthritis It is of course, widely believed that the streptococcus infections have a capacity to produce a predisposition or tendency to arthritis —Ed.]

Serologic Studies in Experimentally Produced Polyarthritis Lofstrom recently described a substance which he designated as nonspecific capsular swelling substance It appears in the serum in various diseases including rheumatic disorders and gives a nonspecific swelling reaction with type XXVII pneumococci The substance was identified by Lofstrom with the acute phase protein described by Tillet and Francis in 1930 Electrophoretic experiments have shown that it belongs to the alpha globulins A similar substance giving a reaction with type XVI pneumococci occurs in rabbit serum

In the present experiments reported by Per Hedlund and Gunnar Lofstrom[1] (Stockholm) attempts were made to induce infectious polyarthritis by intradermal and intravenous injection of small nonlethal doses of living hemolytic streptococci isolated in a case of scarlet fever Serologic examination included determinat F

(1) Acta med S and 544 1946

phase protein level agglutinins antistreptolysin and complement titer The animals used in the experiments were rabbits

After intradermal inoculation local inflammation developed at the site of injection and in some animals abscesses formed but no sepsis and no joint changes occurred Acute phase protein appeared in the serum of most animals the reaction remaining positive for several days after injection the antistreptolysin titer was increased agglutinins were not demonstrated and the complement titer fell during the second month of the experiment In several animals given intravenous injections joint changes consisting of exudation and swelling of the synovial membrane developed As the joint symptoms developed serum antistreptolysin rose considerably Cultures of blood and joint material obtained at autopsy one month after injection remained sterile Animals in which polyarthritis did not develop had a fairly low antistreptolysin titer throughout the observation period All animals produced acute phase protein No agglutinins appeared during the first two months

Possible Relationship of Pleuropneumonia like Organisms to Reiter's Disease Rheumatoid Arthritis and Ulcerative Colitis Robert Wallerstein Bert Vallee and Louis Turner[2] (Mount Sinai Hosp New York City) carried out a series of agglutinations on the erums of 102 patients for titers against one strain of pleuropneumonia like organisms (strain no 350) Control patients and those with rheumatoid arthritis ulcerative colitis and other chronic arthritic and diarrheal diseases did not show significant titers against the strain used This was true in both active and quiescent cases

Significant titers (higher than 1 16) were obtained only in some of the small group of patients with probable Reiter s syndrome (two of three) and in some of those with various symptom complexes resembling larval forms of this syndrome (two of five) The latter presented various combinations of colitis arthritis conjunctivitis

(2) J I f ct. D 79 134 140 S pt Oct 1946

urethritis or cervicitis and skin lesions However no conclusion as to the possible relationship of this group of cases to true Reiter s disease can be drawn since four of the five patients were women and no well substantiated case of the syndrome has as yet been described in a woman

Although only four of eight in this group had significant titers against strain no 350 and no positive titers were obtained in patients with uncomplicated arthritis or colitis it must be pointed out that the various strains of pleuropneumonia like organisms thus far identified uniformly show great antigen antibody specificity with almost complete failure to cross agglutinate other strains even those isolated from the same animal species If as seems likely multiple human strains are eventually identified and fail to show cross agglutination phenomena to rule out contact by a human being with pleuropneumonia like organisms his serum would have to be agglutinated against each of these strains separately The present results are reported to call attention to the suggestive data linking this group of organisms to a variety of human ailments such as the chronic and acute arthritides and their common associated manifestations

BRUCELLOSIS

Brucellosis Advances in Diagnosis and Treatment are discussed by *Harold J Harris*[3] *(New York City)* Acute brucellosis should be considered when there are persistent or intermittent high fever sweating palpable spleen great fatigue and joint or muscle pain and typhoid and malaria have been ruled out Next to culture agglutination is the most reliable test of active infection In chronic cases a negative agglutination reaction does not exclude brucella infection The intradermal reaction may be negative in 5–10 per cent of cases in which culture is positive The skin test has the same relative significance

(3) J A M A 131 1485 1493 Aug 31 1946

in brucellosis as the tuberculin test in tuberculosis A definitely positive reaction produces an area of induration and redness of more than 5 mm A positive skin reaction and a low to moderate phagocytic index indicate brucel losis from which the patient has not recovered A pos itive skin reaction and a high opsonic index suggest re covery Culture for brucella needs special methods spe cial mediums and special aerobic conditions Brucella melitensis and suis require no carbon dioxide for growth and Brucella abortus requires 10 per cent carbon dioxide All strains grow best in bactotryptose broth or agar or on liver infusion broth or agar Frequent subculturing is essential Since the spleen is the site of localized infection and blood cultures are often negative culture of splenic tissue obtained through a peritoneoscope to prevent hem orrhage seems logical

Localized foci in the spleen gallbladder retroperitoneal and other lymph nodes ovaries and prostate may be inac cessible to treatment Splenectomy is sometimes justified Some phenomena such as arthralgic or arthritic complica tions reactions at the site of vaccine injection and eosino philia may be due to allergy which should be considered in treatment Differentiation between chronic brucellosis and psychoneurosis may be extremely difficult espec ally when the two coexist Psychiatric examination including use of the Rorschach test is then of value

Penicillin is ineffective in brucellosis Streptomycin ap parently terminates the acute phase so that cultures are negative but a relapse usually follows Its use in the chronic form has not been reported Sulfonamides do not cure the acute or chronic illness but may be effective in chronic cases in presence of joint involvement Their greatest usefulness is in terminating the acute phase Of great importance is administration of small doses of sulfonamide for weeks after subsidence of the acute at tack when vaccine treatment is initiated to induce a pro- tective level of opsonic activity before the bacteriostatic effect of the sulfonamides has been lost The same prin ciple applies to streptomycin Brucella vaccine is seldom

successful in the acute phase because of undesirable febrile and focal reactions In Harris experience a vaccine of heat killed Br abortus has been the most effective means of treating chronic brucellosis Use of the intramuscular route rather than the subcutaneous not only produces less local reaction but is more effective in bringing about desensitization and phagocytic response Sufficient dilution is especially important The interval between injections varies from four to seven days depending on the reaction The deltoid is the preferred injection site *Intravenous injections of vaccine should be given* when desensitization and phagocytic response are not *satisfactory Contraindications to the intravenous route* are ocular involvement and disease of the central nervous system Diet in brucellosis should be high in proteins and carbohydrates and low in fats

Streptomycin Therapy in Undulant Fever George H Finch[4] (Des Moines Ia) reports six cases of acute undulant fever of which one is given here All patients had positive blood cultures before treatment was started five for Brucella suis and one for Brucella abortus Daily dose of streptomycin was 5 Gm given intramuscularly in divided doses every three hours Total dose varied from 20 to 51 Gm Although none of the patients had eighth nerve involvement reactions did occur and routine laboratory tests indicated possible injury to liver and kidney

Though the series is too small to warrant final conclusions results were encouraging There were immediate decrease in elevated temperature elimination of subjective symptoms (chills sweats anorexia and muscle weakness) and earlier return of appetite There were no recurrences or relapses after the antibiotic was discontinued and there was a marked decrease in length of convalescence

Man 36 was treated symptomatically at home for several days during which time temperature fluctuated between 100 and 104 6 F Blood culture was positive for Br suis and

(4) Am J Med. 2 485-490 May 1947

agglutination tests were positive for undulant fever in a dilution of 1 320 and negative for typhoid and tularemia The patient was hospitalized and streptomycin therapy begun after 24 days of illness Traces of albumin and crystals were present in the urine during therapy He received a total of 51 Gm. streptomycin Blood cultures were positive on the day therapy began negative on the third fourth seventh and eighth days positive on the ninth day negative on the tenth and eleventh days positive on the first and second days after streptomycin was discontinued and negative on the third day after treatment The patient returned to work on the seventy third day after onset of illness

Finch believes that streptomycin is an excellent therapeutic agent for treatment of acute undulant fever

DENGUE

Control of Dengue in Hawaii An epidemic of dengue fever started in Hawaii in July 1943 Its control is reported on by Charles L Wilbar Jr[5] (Board of Health Hawaii) No dengue had been reported since 1912 in Hawaii The usual history of dengue newly introduced into a community where the Aedes mosquito thrives has been spread to 50–75 per cent of the population Because Hawaii was an important military center the United States Army and Public Health Service assigned 398 persons to full time mosquito control activities The peak of the epidemic was reached at three months and then gradually declined for six months Among the 250 000 persons in Honolulu 1 496 contracted dengue Only two persons outside the city were affected

The Aedes mosquito carrier of dengue was attacked by all established methods plus use of DDT and fogging of the air around homes of dengue patients with insecticide sprayed at high pressure from tank trucks Newspaper articles radio broadcasts handbills door to door canvass and talks by health department staff to clubs were all used to disseminate mosquito control information

When a case was reported the home was visited by a

(5) Am. J Pub Health 37 663 674 Jun 1947

public health nurse and a mosquito inspector Mosquito breeding places i e tin cans bottles and plants that hold water were destroyed and the home sprayed with pyrethrum insecticide A net was kept over the patient for the first four days of illness the period during which mosquitoes obtain the disease

Waikiki where the outbreak originated was placed off limits to army and navy personnel and civilians were urged to stay away if possible Mosquito breeding places were eradicated and the whole area was clouded with *pyrethrum Airplanes and ships leaving Hawaii were* sprayed School grounds were scrutinized for mosquito breeding areas and the classrooms were used for dissemination of information about mosquito control Within two months the Aedes breeding index i e the number of premises found breeding this mosquito per 100 premises examined diminished from 5 7 to about 1 at which point it remained

Experimental Studies of Bullis Fever and Dengue Fever are reported by H R Livesay D J Wilson M Pollard and J C Woodland[6] (M C U S A) Three healthy male volunteers were studied Two were inoculated subcutaneously with 1 cc yolk sac propagated tick strain of Bullis fever agent and one was inoculated subcutaneously with 2 cc whole blood from a patient with Bullis fever On the fourth day after inoculation the three volunteers had symptoms of Bullis fever generalized malaise leukopenia headache *generalized lymphadenopathy and* mild fever Twenty seven days after defervescence each subject was inoculated intradermally with 0 4 cc dengue infected human serum In addition a normal control was inoculated with the dengue fever material A typical syndrome of dengue fever developed on the sixth or seventh day after inoculation in all four subjects This was characterized by generalized malaise headache leukopenia and generalized rash The experiments demonstrated that there is no relation between Bullis fever and dengue fever

(6) Am J Trop Med 26 379 381 July 1946

New Tellurite Plating Medium and Some Comments on Laboratory Diagnosis of Diphtheria As an out growth of four years of practical u e of tellurite plates in detection of diphtheria carriers J Howard Mueller and Pauline A Miller[7] (Boston) u e a formula which is based on the known growth requirements of members of the diphtheria bacillus group and is still makeshift in certain respects None of the ingredients is sharply critical from the quantitative aspect

Composition of Medium

Ag r B

	Qu nt t es 500 Ml. Gm
Agar	10 0
Casamino acids technical	10 0
Commercial casein	2 5
KH PO	0.35
MgSO 7H O	0 05
Tryptophane	0 025
Water to 500 ml.	

Ser m Tel ur So u on

	S oc So u ion S ici n fo 4 L M d um
Sodium lactate solution	40 0 ml
Ethyl alcohol	10 0 ml
Calcium pantothenate	0.2 mg
Sterile horse or beef serum	50 0 ml
Potassium tellurite	0 4 Gm.

Technic —The stock solution of serum tellurite should be made first The sodium lactate is put in a suitable container and sterilized in the autoclave After cooling and under terile conditions the alcohol calcium pantothenate autoclaved in a few milliliters of water serum and potassium tellurite dis solved in a few milliliters of sterile water are successively added with thorough mixing after each addition The solution is well stoppered and stored in the cold room Excessive heating is avoided The agar base should be freshly prepared for each batch of plates The ingredients listed are mixed in a flask and the pH is adjusted to about 7 6 If the dehydrated base is available 22 5 Gm. i simply added to 500 ml water In either case the flask is heated to boiling with frequent

(7) J B ct 51 743 750 J 1946

shaking transferred while hot to the autoclave and sterilized at 10 lb steam pressure for 10 minutes The sterilized solution is cooled to about 50 C and 12 5 ml serum tellurite solution is added Reasonably thick plates (20 ml) are poured and allowed to cool without covers for a few minutes their surface must be dry

Each plate is marked off in sections with a wax pencil and 6 8 or even 12 swabs may be cultured on the standard Petri dish After 15-18 hours incubation the plates are examined Easily visible confluent growth should be apparent in cultures of swabs from the throat of a patient with a fresh infection of the mitis or gravis type Plates showing no growth are reincubated and again examined at 24 and finally 48 hours when mitis colonies are 1-1 5 mm in diameter black and convex with a glistening surface The gravis type is larger 2-3 mm in diameter is flat with somewhat irregular edges (seldom typical daisyhead) and has a dull surface and a slate gray color Even in 18 hours with a strongly positive culture the difference in appearance of typical mitis and gravis growth is already detectable The intermedius colonies are relatively minute pinpoint in size at 24 hours and 0 2-0 3 mm in diameter at 48 hours They show little darkening but if the plate at 48 hours is laid on a sheet of white paper in a good light they are definitely brownish gray They appear as fine flat colonies with a central knob and a slightly crenated periphery

Diphtheria cannot be diagnosed in the laboratory The bacteriologist may be able to state after a delay of 12-15 hours that organisms which he believes are consistent in morphology with Corynebacterium diphtheriae are present in his culture The diagnosis is up to the physician

Treatment of Acute Diphtheria and Chronic Carrier State with Penicillin is reported by Louis Weinstein[8] (Boston) Daily cultures of both nasal and pharyngeal mucosa were carried out for all patients from time of hospital entry until discharge In 12 patients with diphtheria treated by antitoxin alone the average time required for disappearance of Corynebacterium diphtheriae from nose and pharynx was 33 25 days Twenty six patients with diphtheria were treated with penicillin in addition to antitoxin The first three patients were given 120 000 units daily for a total of 330 000 units The dose was then increased to 120 000-240 000 units daily for 12 days

(8) Am. J M S 213 308 314 March 1947

For the 23 patients treated with the larger dose the average time required for disappearance of C diphtheriae was 3 96 days

Thirteen chronic carriers of C diphtheriae were treated with penicillin Administration of 240 000 units daily for 12 days eliminated C diphtheriae in 3–4 days but smaller doses produced only slow clearing of the carrier state

No striking alteration could be detected in the clinical course of acute diphtheria treated with penicillin plu antitoxin and that treated with antitoxin alone The out standing difference between the two groups was a marked reduction in time required for the causative organism to disappear from the nose and pharynx in those treated with penicillin The average time of 3 96 days for clearance of the organism from patients treated with both penicillin and antitoxin seems to make tenable the conclusion that treatment with penicillin is effective in shortening the carrier state in the acute stage of diphtheria

Penicillin in Treatment of Diphtheria and Diphtheria Carriers in five hospitals in the European theater of op erations was studied by Samuel Karelitz Lewis R Was serman and Ralph E Moloshok[9] (New York City)

Method —Because penicillin is not a substitute for anti toxin all patients suspected of having diphtheria were given 40 000 units of antitoxin intramuscularly and if clinically indicated 20 000 additional units intravenously Immediately after material for culture was taken from the throat penicillin administration was begun in four hospitals as follows (1) 20 000 units intramuscularly every three hours (2) 20 000 units intramuscularly every two hours (3) nose and throat spray hourly during the day and every three hours at night with a solution of 1 000 units per cc of physiologic sodium chloride solution (4) 20 000 units intramuscularly every three hours plus nose and throat spraying hourly the first day and every three hours thereafter In the fifth hospital control patients received antitoxin but no penicillin Penicillin therapy was continued until three consecutive daily throat cultures were negative Thereafter throat material was cultured daily for three days every second day for six days and every third day for nine days

Only 2 of 21 patients with faucial diphtheria treated

(9) J P diat 30 18 28 J nuary 1947

with penicillin by nose and throat spray for seven days had cultures negative for *Corynebacterium diphtheriae* within that period Comparison of controls and patients given penicillin intramuscularly revealed that throat cultures were positive for 27 5 per cent of 80 penicillin treated patients and 100 per cent of 42 controls 5 days after onset of disease 7 5 per cent of penicillin treated patients and 92 8 per cent of controls 10 days after onset and less than 5 per cent of penicillin treated patients and 85 7 per cent of controls 15 days after onset

Eight control patients who were convalescent carriers for 26–30 days were given penicillin nose drops every 3 hours for 7 days all ceased to be carriers within 7 days However only 2 of 13 patients who had previously received penicillin intramuscularly were cleared of *C diphtheriae* in 7–23 days of local therapy Ten of 14 carriers were cleared of *C diphtheriae* within four to six days by 20 000 units of penicillin given intramuscularly every three hours

Diphtheric membrane persisted for equal lengths of time in control and treated patients Faucial edema and subjective sore throat were favorably influenced by penicillin The authors believe that incidence and severity of complications due to pyogenic organisms were less in penicillin treated patients although penicillin was ineffective in preventing toxic complications of diphtheria

Results in all groups were too similar and the groups too small to warrant conclusions as to which dosage was more effective However results do illustrate that intramuscular use of penicillin was effective in eradicating infection in acute faucial diphtheria whereas nose and throat sprays failed in all but two cases The authors stress that penicillin should not be used as a substitute for diphtheria antitoxin

Penicillin in Treatment of Diphtheria David A Long[1] reports dramatic results in three patients with diphtheria who were given 1 million units penicillin daily Long believes that a smaller dose would probably have

(1) Brit M J 1 884 886 J 1 1947

been inadequate but that a larger dose would have been even more effective He stresses administration of adequate amounts of antitoxin One case is given here

Man 20 seen at 3 30 p m on the fourth day of the disease was ashy gray and cyanosed He had a massive bull neck pain and severe dysphagia. Breathing was partially obstructed and thick sputum was coughed up with difficulty An adherent membrane covered the fauces tonsils and uvula Swelling obstructed the postnasal space He had been given 100 000 units of antitoxin intramuscularly the previous day Penicillin was given every three hours for three days in amounts of 1 million units daily At 11 30 a m the day after penicillin was started his face was pink and he was nontoxic and felt better The active glistening edge of the membrane had dulled and it was no longer adherent The bull neck had reduced in size On the third day the membrane separated He recovered without complication Corynebacterium diphtheriae gravis were isolated on the first day of the disease but daily swabs of the membrane thereafter failed to reveal organisms The organism was inhibited by 0 02 units of penicillin

Equally striking results were achieved by similar treatment of two other patients The evidence presented indicates that it is possible to remove diphtheria bacilli from the upper respiratory tract within 24 hours with 1 million units of penicillin daily

Penicillin in Treatment of Severe Diphtheria Richard J Dodds compares results obtained in 13 patients treated with antitoxin and 14 patients treated with a combination of antitoxin and penicillin The penicillin treated patients comprised a majority of those with severe diphtheria hospitalized during 1945 and January 1946 The patients treated with antitoxin were comparable as far as possible in respect to age and comprised the remaining patients with severe diphtheria and a few with less severe involvement admitted during the same period Penicillin was given every three hours intramuscularly 200 000 units was given daily for two days in the first cases and approximately 100 000 units daily for three to five days in later cases The disease was confirmed bacteriologically by swabbing the lesions

Results indicated that penicillin has little effect on rate

( ) B M J 2 8 10 July 6 1946

of clearance of membrane but does reduce incidence of complications Paralysis and myocardial involvement both occurred much less frequently in penicillin treated patients Penicillin therapy shortens the toxemic state in nearly all cases and reduces the length of stay in the hospital Whereas penicillin in no way supplants antitoxin the author believes it should be given with antitoxin to all patients with severe diphtheria

Cutaneous Tests and Immunization in Diphtheria and Scarlet Fever A survey of 20 years of cutaneous testing and immunization of student nurses at the contagious department of Cleveland City Hospital is reported by John A Toomey and Robert A Keller[3] (Western Reserve Univ) During this period all student nurses were given Schick and Dick tests and those with positive reactions immunized Of more than 5 000 Schick tests done approximately 50 per cent were positive Schick tests were positive in 50 9 per cent of nurses from Cleveland hospital and in 46 4 per cent of nurses from hospitals in smaller communities They were negative in 55 5 per cent of nurses who had a history of diphtheria and in 49 7 per cent of those without such a history Many of the nurses who had had diphtheria may have been potentially immune and needed only a stimulating dose of toxin to raise the antibody titer A year after recovery from diphtheria a much higher rate of negative reactions would probably have been found

Toxin antitoxin contains horse serum which may cause sensitization This is a particularly serious problem among student nurses who are heavily exposed to diphtheria and may contract the disease despite immunization In such an event diphtheria antitoxin may cause serum reaction In addition toxin antitoxin often takes a year to effect immunity Ramon eliminated horse serum from his antigen by detoxifying the toxin with formaldehyde The more recent alum precipitated toxoid promises to be superior to its two predecessors The over all failure rate in diphtheria immunization was 14 6 per cent The failure rate was

(3) Am J Dis Child 73 531 44 May 1947

lower with toxoid and with alum precipitated toxoid than with toxin antitoxin Five per cent of those immunized had undesirable reactions nearly all of which consisted of soreness and induration at the injection site The least reactions resulted from toxin antitoxin and the most from toxoid The authors administered 0 1 cc alum precipitated toxoid routinely as a test dose If no untoward reactions occurred 0 4 cc. was given the next week and 1 cc the next month to all subjects with positive Schick reactions They consider alum precipitated toxoid the agent of choice

Of 6 500 student nurses given the Dick test 61 1 per cent had negative reactions Of nurses who had had scarlet fever 76 2 per cent had negative reactions whereas 57 8 per cent of those without a history of scarlet fever had negative reactions For no apparent reason nurses from hospitals in smaller communities had a higher rate of negative reactions to the Dick test than did nurses from Cleveland hospitals Scarlet fever occurred under heavy exposure in 1 8 per cent of those who originally had negative reactions to the Dick test Those with positive reactions were given five weekly doses of toxin containing 500 2 000 8 000 25 000 and 100 000 cutaneous test doses Doses were split and given over extended periods when reactions were encountered early in the course of immunization Immunization was performed on 2 162 nurses and of these 89 1 per cent subsequently had negative Dick reactions Reactions occurred in 28 7 per cent of those immunized and varied from mild local soreness to scarlet fever in miniature

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ENCEPHALITIS

Epidemic Encephalitis in the Far East A Review is presented by Joel Warren[4] (S C A U S) Two types of acute encephalitis caused by filtrable virus are endemic in

(4) Am. J T op M d 6 417 436 J ly 1946

the Far East Japanese B encephalitis and Russian spring summer encephalitis The Russian autumn encephalitis occurring in eastern Siberia is identical with Japanese B encephalitis

Japanese B encephalitis has been endemic in Japan since 1870 It has also been observed in Siberia Korea Ryukyu Islands Formosa China and the Maritime Krais it has never been reported in the Philippine Islands The disease occurs during the hottest part of summer and in early autumn There is about 50 per cent mortality Incidence is highest in the older age groups The disease affects persons of all walks of life It is mosquito borne the most susceptible species being Culex pipiens Aedes togoi and Aedes esoensis Experimental transmission has been accomplished in species indigenous in the United States i e C pipiens Culex quinquefasciatus Aedes nigromaculis Aedes lateralis and two species of Culiseta The natural reservoir for the virus is the blood of dogs and probably of other domestic animals

The incubation period of Japanese B encephalitis is six to eight days The disease may begin abruptly or after a prodromal period of malaise headache and chills The symptoms are those of meningoencephalitis Coma is frequent and tremors of tongue and hands are common ocular disturbances are not as frequent as in lethargic encephalitis Extensive sequelae are rare and parkinsonism is extremely rare The virus is readily isolated from the brain spinal fluid and blood and is sometimes detectable in the urine The best method of isolation is intracerebral inoculation into Swiss mice Adult mice are resistant to peripheral inoculation Other susceptible animals are the Syrian hamster monkey and sheep A vaccine developed from infected mouse brain produces neutralizing antibodies in man There is no specific therapy for the disease

Russian spring summer encephalitis is endemic in northern Siberia and Russian territories The victims are almost always persons working in virgin forests who are exposed to infected blood sucking ixodid ticks There is no evidence that the disease is spreading to new areas It is the only

known virus disease of man in which the bite of an infected tick is the main mode of transmission. Ixodes persulcatus Haemaphysalis concinna Dermacentor silvarum and probably Haemaphysalis japonica are the carrier ticks I persulcatus being the major vector The principal hosts on which these arthropod feed are the smaller forest rodents

Seventy five per cent of patients give a history of tick bite 8–18 days before onset of symptoms Onset is abrupt The disease characteristically involves the part of the central nervous system innervating the cervical and brachial musculature and results in paralysis of the shoulder girdle Paralysis most commonly occurs on the second or third day of the disease Death usually follows involvement of the respiratory center The mortality rate for nonvaccinated patients is 30 per cent Residual paralysis of the neck and shoulder girdle occurs in 20 per cent of cases The main pathologic findings in Russian spring summer encephalitis are inflammatory and degenerative changes in the brain cord sympathetic nervous system and peripheral nerves The virus is present in the circulation during the acute phase and has been isolated from the spinal fluid Susceptible animals are mice hamsters and monkeys The prophylactic vaccine is prepared from infected mouse brain in which the virus has been inactivated with formaldehyde Convalescent human serum inoculated intrathecally has been recommended for treatment of the disease The virus of louping ill restricted to Scotland and northern England and occurring only in sheep is closely related perhaps identical with the virus of Russian spring summer encephalitis There is no cross immunity between the latter and the St Louis strain of encephalitis The virus of Japanese B encephalitis is related to but readily distinguishable from the St Louis variety

Herpes Simplex Encephalitis Report of Two Fatal Cases is presented by Loring Whitman (M C A U S) Margaret J Wall (Washington D C) and Joel Warren[5] (S C A U S) One case is given here

(5) J A M A 131 1408 1411 A g 4 1946

of jaundice but continued for approximately 10 days in moderate and 4–5 weeks in severe cases Despite pro found nausea in some cases vomiting was not prominent and rarely occurred after appearance of jaundice After jaundice appeared the subsequent course was that of infective hepatitis In severe cases convalescence was prolonged and even in milder cases debility seemed out of proportion to severity of the disease Laboratory in vestigations in the more severe cases revealed secondary anemia and hyaline and granular casts in the urine There were no deaths

Although a vaccine contaminated by the virus of epi demic hepatitis seemed the most probable source certain cases may have resulted from contact infection It is otherwise difficult to explain the selective way in which the hospital staff was affected

Jaundice Hepatocellular Catarrhal Icterus and Hepa titis Following Use of Yellow Fever Vaccine Clinico-pathologic Comparisons I W Held and A Allen Gold bloom[5] (Beth Israel Hosp New York City) state that hepatocellular catarrhal icterus and postvaccinal hepatitis are symptomatically alike Duration of the prodromal stage in catarrhal icterus is six to nine days considerably shorter than in postvaccinal hepatitis in which gastro-in testinal symptoms may precede jaundice by several weeks The average course of hepatocellular catarrhal icterus is five or six weeks with complete and rapid recovery In postvaccinal hepatitis although jaundice may not be pro-nounced convalescence is extremely slow The patient may have disturbed appetite slight secondary anemia and elevation of blood bilirubin for several months

Postvaccinal hepatitis is most likely due to a virus con tained in some stocks of vaccine for yellow fever Patho logically postvaccinal hepatitis is a true hepatitis but fortunately is reversible in most instances

The simple Volhard water test of urinary output is of great diagnostic and prognostic value if there is no

(5) New Y k State J Med. 44 270 279 F b 1 1944

in the mean end points were significant made it possible to establish a reproducible standard of chicken red cell agglutination activity based on a unit weight of purified virus material As a result it was possible to devise a standardized procedure for carrying out with high accuracy quantitative measurements of influenza virus

Ultracentrifugal, Chemical and Electron Microscopic Identification of the Influenza Virus was studied by J W Beard D G Sharp A R Taylor I W McLean Jr Dorothy Beard A E Feller and John H Dingle (Duke Univ) Their results show that influenza viruses A (PR8 strain) and B (Lee strain) and the swine influenza virus can be concentrated by adsorption on and elution from chicken red blood cells followed by ultracentrifugation at 20 000 g or by ultracentrifugation at 20 000 g alone This was established by biologic behavior of the concentrates which was identical with the behavior of the three types of virus investigated Characters of the concentrates with respect to purity and nature were determined by examination with the analytic ultracentrifuge and electron microscope and by chemical analysis

Electron micrographs of purified preparation showed images of particles of widely variable size and shape but similar morphology Evidence of mean size and of degree of variation in size furnished by the micrographs was substantiated by ultracentrifugal data The micrographs also showed internal differentiation within the virus particles

Variation in particle size and shape is clearly incompatible with the hypothesis that the influenza virus may be molecular in nature Instead the findings resemble results which would be expected from a similar examination of a pure culture of small coccobacilli A further parallelism is the internal structure within the particles structure which is not greatly different morphologically from that seen in electron micrographs of bacteria The chemical constitution of the influenza virus is likewise

(8) S th. M J 37 313 320 J 1944

plasmosis Abdominal exploration because of upper abdominal pain revealed some enlargement of spleen and liver Examination of liver tissue obtained by biopsy revealed organisms resembling the causative organism of histoplasmosis He recovered from the operation and returned home two weeks later where he received a course of antimony potassium tartrate but died in 11 weeks Blocks of tissue and the intact heart were examined post mortem Occupying fully three fifths of the surface of the mitral valve was an organized vegetation which extended down onto the chordae tendineae There were smaller warty vegetations on the free edge of one aortic cusp Histologically there was definite evidence of old rheumatic fever in the myocardium and at the base of the valves Enmeshed in the vegetations were myriads of yeast like organisms which had the typical appearance of Histoplasma capsulatum Similar organisms were demonstrated in the reticulo endothelial cells of the spleen

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INFLUENZA

Quantitative Aspects of Red Blood Cell Agglutination Test for Influenza Virus Gail Lorenz Miller and W M Stanley[7] (Rockefeller Inst Princeton N J) conducted a detailed study of the nature of the variable inherent in the chicken red cell agglutination test for influenza virus in an effort to obtain a method of measurement of biologic activity of sufficient accuracy that it might be used as a reliable index of chemical purity of preparations of the virus It was found that the temperature at which the test is conducted has a marked effect on the titer whereas within the range of pH 6–8 the pH has a negligible effect A variation in results may be encountered due to a variation in the specific behavior of red cells from different chickens and to an instability of the red cells themselves Preparations of purified influenza virus held at 4 C on the other hand were found to be stable with respect to chicken red cell agglutinating activity for several months This and the fact that in duplicate measurements on different samples the accuracy was such that the chances were 19 out of 20 that differences of 8 4 per cent

(7) J E per Med 79 185 195 F bru ry 1944

in the tissues of the embryo in a certain fixed amount

Effect of Virus Rendered Noninfective by Ultraviolet Irradiation on Multiplication of Influenza Viruses in Chick Embryo—James E Ziegler Jr (M C U S N R) George I Lavin and Frank L Horsfall Jr (M C U S N R) found influenza A or B virus rendered non infective by ultraviolet irradiation capable of producing interference with multiplication of active influenza viruses in the chick embryo A theory that infection by influenza virus is mediated by a cell receptor substance was ad vanced by Hirst It seems possible that such a receptor substance could be reactive with either active virus or inactive virus if the latter retained the particular struc tural configuration required Interference might then re sult from quantitative saturation of the receptor substance of susceptible cells whether the point of saturation was achieved by multiplication of small amounts of active virus or by introduction of large amounts of virus either active or noninfective Consequently it seems reasonable to assume that reciprocal interference between influenza viruses depends on some portion of the virus particles capable of reacting with susceptible cells possessed in common by influenza A influenza B and swine influenza viruses and relatively resistant to ultraviolet irradiation Regarding the nature of this portion of the virus particle there is as yet no evidence

Evaluation of Methods for Concentration and Purifi cation of Influenza Virus W M Stanley (Rockefeller Inst Princeton N J) studied differential centrifugation in a vacuum type centrifuge adsorption on and elution from adult chicken red cells elution of the precipitate formed on freezing and thawing of allantoic fluid adsorp tion on and elution from embryonic chick red cells and combinations of the first method with each of the three succeeding ones Over all yields of virus of 50–70 per cent were obtained by these methods and combinations

(1) J E pe M d. 79 379-400 Ap 1 1944
(2) Ib d pp 255 266 M b 1944

similar to that of certain bacteria in content of protein and fat and of carbohydrate in excess of that bound in nucleic acid

The results provide definite evidence that the influenza virus is not molecular Though its exact biologic status is yet to be determined it appears desirable to consider it tentatively as an obligate parasite closely related other wise to certain bacterial micro-organisms

Interference between the Influenza Viruses—*Effect of Active Virus on Multiplication of Influenza Viruses in Chick Embryo*—James E Ziegler Jr and Frank L Horsfall Jr (M C U S N R) demonstrated reciprocal interference between influenza A influenza B and swine influenza viruses This constitutes additional evidence that the interference phenomenon can under certain conditions be demonstrated between antigenically distinct viruses Under conditions of the experiment any one of the three virus strains when first introduced in the embryo regularly interfered with multiplication of either of the other two viruses inoculated somewhat later provided certain limits of time and quantity were not exceeded This finding suggests that basic mechanisms responsible for production of interference were in each instance similar Available evidence does not indicate that interference resulted from interaction of one virus with another nor did presence in the chick embryo of multiplying virus per se interfere with multiplication of another virus It seems reasonable that the state responsible for interference was induced by an alteration in the susceptible tissues of the chick embryo which followed establishment of the initial virus infection Reversal of the direction of interference in which multiplication of the initially inoculated virus is inhibited by simultaneous or later addition of very large amounts of another virus would seem to offer evidence of the quantitative nature of the interference It also suggests that between two viruses involved in interference there may be competition for a substance which is present

(9) J Exper Med 79 361 377 April 1944

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(1) J E pe M d 79 379-400 Ap il 1944
(2) Ibid pp 255 266 M ch 1944

except for somewhat lower yields when adsorption on and elution from adult chicken red cells was used However purified products obtained by methods involving only use of red cells or freezing and thawing technic were found to contain about 80 per cent of nonvirus protein The purified products obtained when differential centrifugation was used either alone or in combination with any one of the other methods were found to be indistinguishable and to consist of a fairly homogeneous component having a sedimentation constant of about 600 S Such preparations possessed about 22 000 chicken red cell agglutinating units per mg protein nitrogen and solutions containing only about 10 Gm of the materials gave 50 per cent infectivity end points in chick embryos The Sharples centrifuge was almost as efficient as the vacuum type centrifuge for concentration and purification of influenza virus and because of its larger capacity is recommended for preparation of purified virus on a large scale

Effect of Some Chemicals on Purified Influenza Virus C A Knight and W M Stanley (Rockefeller Inst Princeton N J) studied effects of 0 05 and 0 5 N solutions of 20 different chemicals on activity of purified PR8 influenza virus in 0 1 M phosphate buffer Tests in chick embryos and mice showed that virus activity was destroyed by strong oxidizing agents such as iodine by salts of heavy metals by mercurochrome by formaldehyde and by the detergents phemerol roccal and sodium dodecyl sulfate Reducing agents appeared to have little if any inactivating effect with the exception of 0 05 N ascorbic acid At concentrations tested sulfathiazole sodium exerted only a weak inactivating effect Phenol in 0 5 N concentration inactivated the virus promptly but solutions of the strength more commonly used for bactericidal purposes were only weakly virucidal The virus appeared relatively unaffected by glucose ammonium sulfate calcium chloride sodium thiosulfate and arginine

(3) J Exper Med. 79 291 300 March 1944

Cutaneous Reaction to Influenza Viruses W I B Beveridge and F M Burnet (Melbourne) report that intradermal injection of a 1 10 dilution of unheated or boiled allantoic fluid infected with influenza virus A or B produces a cutaneous reaction in most adults and some children Similar reactions are not produced by normal allantoic fluid or by suspensions of chick tissue containing 10–20 times as much protein as the influenza reagent Partial purification of the virus does not diminish its capacity to produce reactions In adults the size of the reaction bears no correlation to the serum antibody titer

Among 31 children tested intradermally with influenza A and B reagents there were 18 reactions and in all but 1 child serologic tests revealed previous infection by corresponding viruses However in many instances children who gave positive reactions to serologic tests failed to give appropriate skin reactions

The authors suggest that allergy to the virus may play a part in resistance to infection and when infection does occur in production of symptoms

Clinical Evaluation of Vaccination against Influenza. Preliminary report of a study on approximately 12 500 men in Army Specialized Training Program units throughout the country is presented by members of the Commission on Influenza Board of Investigation and Control of Influenza and Other Epidemic Diseases in the Army Preventive Medicine Service Office of the Surgeon General United States Army The vaccine was prepared in laboratories of biologic firms according to specifications of the Commission Each 1 cc of vaccine was made up of 0 5 cc representing type A virus recovered from 5 cc. allantoic fluid and 0 5 cc representing type B virus recovered from 5 cc allantoic fluid The type A component represented equal parts of the PR8 strain and of the Weiss strain isolated in May 1943 The type B component contained only the Lee strain Control material consisting

(4) M J A t alia 1 85 89 J n. 29 1944
(5) J. A. M. A 124 982 985 Ap 1 1944

of isotonic solution of sodium chloride to which 1 5 000 formaldehyde solution and phenyl mercuric nitrate 1 100 000 were added was prepared bottled and subjected to the same tests for sterility

Each company or organization within a unit was divided so that alternate individuals received respectively vaccine and control material One dose of 1 cc was given subcutaneously After vaccination was completed records were removed so that on subsequent visits the observer had no information as to whether a patient belonged to the vaccinated or the control group Prior to vaccination and throughout the observation period close observation of all individuals reporting to sick call was maintained and the same type of record card was used throughout An effort was made to gain uniformity in designation of cases by accepting for diagnosis of influenza those in which illness was of rapid onset with mild upper respiratory complaints chilliness aches and prostration and admission temperatures were 100 F or more without obvious evidence of other disease

Vaccination done shortly before or even after onset of the recent epidemic of influenza A was found to exert a protective effect with a total attack rate of 2 22 per cent among 6 263 vaccinated individuals and 7 11 per cent among 6 211 controls a ratio of 1 3 2 Influence of vaccine was most clearly evident at the height of epidemic prevalences Duration of effect has not been determined

Immunity in Human Subjects Artificially Infected with Influenza Virus, Type B Epidemiologic evidence indicates that immunity to influenza is acquired by the human subject presumably as the result of infection but its duration has not been clearly established Thomas Francis Jr Harold E Pearson Jonas E Salk and Philip N Brown[6] studied the reaction of a group of individuals to induced infection with influenza virus type B and determined their response to the same virus four months later The Lee strain of influenza virus type B

(6) Am. J P b Health 34 317 334 Ap il 1944

was used throughout Subjects tested were ambulatory males residents of one ward of Ypsilanti Mich. State Hospital Many were in older age groups confined to the ward except for a daily walk outdoors No selection was made on the basis of serologic tests There had been no evidence of heightened incidence of respiratory disease in the previous eight months All were carefully examined for signs of acute respiratory illness before inclusion in the group

Inhalation of finely dispersed type B influenza virus resulted in a high incidence of clinical infection resembling a mild form of the natural disease Four months later 24 of the same subjects received a second inhalation of the same virus Fever symptoms and serologic responses were noted The illness was milder in most of the pre viously infected individuals than in controls inoculated at the same time Few were refractory to reinoculation The diminished response to reinfection was most evident in those who had the highest fevers at the first test Nevertheless evidence indicates that mild primary in fections were as beneficial as the more severe ones Al though there was a trend toward association between high antibody titers and low temperatures no uniform correlation between antibody titer of an individual and his response to inoculation was found

***Influenza among Immunized and Unimmunized Popu*lations in 1943** Groups of persons were immunized with concentrated influenza A vaccine in various centers in Canada from November 1942 through January 1943 A similar number of controls received injections of saline During January there was no sign of an epidemic of upper respiratory tract infection Early in February cases of an influenzal nature appeared in Toronto and in a military camp about 90 miles away During the rest of February and in March cases were observed in *all* the centers where immunization had been carried out Ronald Hare Dorothy M Stamatis and Jocelyn Jackson (Univ

(7) Canad. J P b H lth 34 442 45 Oct ber 1943

TABLE 1.—Results of Tests on Pairs of Serums from Cases of Upper Respiratory Tract Infection in Immunized and Control Groups

Place	No.	Febrile Cases: No.	No. Not Complete	Diagnostic Rise in Antibody for Influenza A +	A ±	B +	B ±	Afebrile Cases: No.	No. Not Complete	Diagnostic Rise in Antibody for Influenza A +	A ±	B +	B ±
Toronto													
Connaught*													
Immunized	77	8	0	0	0	2	1	19	0	0	0	3	3
Controls	9	7	3	0	0	3	0	2	0	0	0	0	0
Students													
Immunized	30	11	2	0	0	2	0	19	4	0	1	1	4
Controls	14	5	3	0	0	2	0	9	2	0	0	3	1
Totals	89	31	8	0	0	9	1	49	6	0	1	7	8
Per cent						37 5	4 1					16 2	18 6
Winnipeg													
Immunized	5	5	0	0	0	2	1	0	0	0	0	0	0
Controls	6	5	0	0	0	1	0	1	0	0	0	0	0
Totals	11	10	0	0	0	3	1	1	0	0	0	0	0
Per cent						30 0	10 0						
Edmonton													
Immunized	23	13	2	0	0	5	2	10	3	0	0	0	3
Controls	12	6	1	0	0	0	0	6	1	0	0	1	0
Totals	35	19	3	0	0	5	2	16	4	0	0	1	3
Per cent						31 2	12 5					8 3	25
Vancouver													
Immunized	4	4	1	0	0	1	1	0	0	0	0	0	0
Controls	2	2	0	0	0	0	0	0	0	0	0	0	0
Totals	6	6	1	0	0	1	1	0	0	0	0	0	0
Per cent						20 0	20 0						
Totals	13[illegible]	66	12	0	0	18	5	65	10	0	0	8	11
Per cent						33 3	9.2					14 2	19.6

*Volunteers from Connaught Laboratories, University of Toronto

of Toronto) with the assistance of C E Dolman P L Rentiers P W Hudson and C R Donovan studied these cases to determine the value of the immunizations

The incidence of infection in both immunized and control groups is given in Table 2 From the serologic results in Table I it will be seen that none of the patients were

TABLE 2—INCIDENCE OF INFECTION IN IMMUNIZED AND CONTROL GROUPS JANUARY TO APRIL, 1943

PLACE	2 DOSES O CO CENTRA V CC		N IMMUNI ED	
	N	N I f ted	No	N I f cted
Toronto	68	30	60	14
Edmonton	85	23	85	12
W innipeg	74	5	85	6
Vancouver	35	4	29	2
Totals	262	62	259	34

infected with influenza A No information as to the value of the vaccine has therefore been obtained There were however more infections in the immunized than in the control groups No explanation for this can be advanced

[However the explanation may be in the interference phenomenon described by Ziegler and Horsfall th s YEAR BOOK p 4?—Ed]

Haemophilus Influenzae Type B Laryngitis with Bacteremia. P G du Bois and C Anderson Aldrich (Children s Memorial Hosp Chicago) report four cases in children of preschool age All four fulfilled the criteria set down by Sinclair for diagnosis of this syndrome acute onset extreme prostration or shock out of all proportion to local observations severe laryngitis with marked edema and hyperemia of both false and true vocal cords fever and marked neutrophilic leukocytosis positive throat culture and bacteremia of Haemophilus influenzae type B Recovery following tracheotomy and adequate sulfonamide therapy was rapid and dramatic in three patients The other child did not have a tracheotomy and had a much prolonged complicated course

The condition is most common in preschool children

(8) J P d t 23 184 188 A g st 1943

Onset is so sudden that it can be dated to the hour Marked prostration defines the condition in contrast to the con dition in ordinary croup Temperature is elevated but drops with tracheotomy and chemotherapy Early surgery seemed to accelerate recovery for in the one patient not operated on temperature remained elevated several days despite chemotherapy All patients displayed marked leukocytosis with an absolute polymorphonuclear increase Differential diagnosis includes consideration of ordinary catarrhal croup foreign body diphtheria postpharyngeal abscess thymic attacks acute edema of the larynx from other causes laryngismus stridulus rupture of a caseous bronchial or mediastinal node into the trachea or bronchus and pertussis

[Of these conditions the influenza laryngitis resembles most closely laryngeal diphtheria but the onset is much more abrupt. —Ed]

MALARIA

Sternal Puncture in Diagnosis of Malaria is described by G J Aitken[9]

Method —A stout lumbar puncture needle may be used cut down to about 2 in with an adjustable stop of glass or metal tubing and a protective rubber buffer at each end to avoid puncture of the mediastinum Site of puncture is the center of the sternum at the level of the second interspace easily localized just below the angle of Louis The needle is inserted vertically through the skin and subcutaneous tissue to bone and firmly pressed through the cortex with small to-and fro rotating movements the butt resting on the thenar eminence and the needle being steadied with the index finger Resistance decreases distinctly when the marrow is penetrated The stilet is then removed and 0 5–1 cc marrow fluid aspi rated Films may be made directly or the fluid ejected into an oxalated tube and examined within half an hour Films are stained by a Romanowsky stain covered with a thin layer of immersion oil and examined with the 1/6 in dry lens and a no 2 ocular Ring and other forms are easily detected and any suspicious object can be quickly scrutinized by the 1/12 in oil immersion lens Long and tedious search of films is

(9) Lancet 2 466-468 Oct. 16 1943

often necessary and preliminary examination of thick drop preparations is often helpful Value of the thick drop method lies in relative rapidity with which the probable result can be reached In Aitken s series no positive result was reported until search of marrow films had confirmed the thick drop findings No extracellular form was recognized as diagnostic

In 10 patients with malarial parasites in peripheral blood sternal punctures were made for comparison Marrow fluid in each case contained a substantially higher proportion of parasite containing cells than did the blood cells In 95 cases peripheral blood examination revealed no erythrocytes containing parasites Of these 35 clinically merited the diagnosis of malaria but had been taking suppressive quinine doses until admission or shortly before and 60 had clinically atypical cases and history of exposure to infection not necessarily recent Of the 35 in the first group sternal punctures were positive in 26 of the 60 with clinically atypical cases sternal punctures were positive in 13 Eight patients with negative sternal punctures were treated successfully with quinine Other diagnoses were made in 48 cases with negative sternal puncture

C A Rumball B G Parsons Smith and Leslie Nancekievill report 38 cases in which diagnosis of malaria was made by sternal puncture These included latent or chronic and acute primary malaria They stress that sternal puncture is an accessory to examination of peripheral blood and does not replace it It is especially valuable in diagnosis of latent malaria presenting obscure illness and may provide a positive diagnosis for some cases of tropical neurasthenia Most pyrexial malarial cases can be diagnosed by examination of peripheral blood but sternal puncture offers a supplement when sporulation is so scanty that peripheral blood parasites seem to be absent

Laboratory Aids in Diagnosis of Malaria. Eric Denhoff (M C A U S) and Bernard C Piper state that laboratory diagnosis of malaria is not difficult but depends on

(1) Lancet 468 469 Oct 16 1943
(2) J Lab & Clin. Med 9 518 5 4 May 1944

good staining technic and examination of blood for parasites at the proper time Field s rapid staining technic of thick smears is ideal when a large number of smears must be examined as quickly as possible Although many authorities feel that blood films should be dried in the horizontal position the authors believe that when Field s stain is used there is definite advantage in drying the smear in the semivertical position The parasites tend to concentrate in one area which diminishes orientation time and facilitates examination

There are two disadvantages to Field s technic (1) If the slide is not washed well some eosinophilic staining debris clings to the slide The examiner soon learns however to differentiate these artefacts from parasites (2) The stain fades making it impossible to keep slides for permanent record It is imperative that the thick smear be not too thick and that the smear is examined at the point where the parasites tend to concentrate

The standard or Wright Giemsa thick smear staining technics are excellent but are not as convenient as the Field technic In a Giemsa stained thick smear the chromatin dot is not as vivid but the cytoplasm is more intense Although it takes more time to stain a thin smear with the Wright Giemsa combination than with a simple Wright stain it is worth while when it is difficult to find a parasite or identify the type of plasmodium present If the slide is stained face down in a Petri dish debris and sediment will fall off and a clean blood film will result

Points in Laboratory Diagnosis of Malaria in China India Burma Theater are described by Irving A Beck (M C U S A) The recommended technic is the combined thick drop thin smear stained with aqueous Giemsa the thick drop *affording rapid diagnosis and the thin* smear serving for species identification when this cannot be made by thick drop alone and for differential white *cell counts* The spirochete of relapsing fever and micro

(3) Rhode Isl nd M J 27 65 67 F bruary 1944

filariae can also be discovered readily on the thick drop

TECHNIC.—Two drops of blood are taken on a clean glass slide One drop slightly larger than that usually collected for an ordinary smear is taken on the first quarter of the slide and a second of usual size at the midpoint. The latter is smeared distally The first drop is evened out to the size of a dime by making a series of widening concentric circles in it with another slide If a small tangential tail is left it will care for excess liquid The slide is allowed to dry in a horizontal position Drying is difficult in humid climates In the field slides can be left in direct sunlight supplemented by fanning If a laboratory is available a drier can be improvised from field equipment. The copper sterilizer is placed in a wooden box the top of which is replaced by the enamel instrument tray with wire or glass rods to hold the slides horizontally Heat generated by steam from the sterilizer when water is just simmering dries the blood in a few minutes Overheating fixes the thick drop and prevents laking of blood subsequently Prompt staining is necessary to deter bacterial growth and mold Thick drops stain best when a few hours old but this advantage has to be sacrificed where mold is a problem Slides must be kept in a box or album or covered with a Petri dish while awaiting examination because growth of mold can occur even on stained blood.

A water bath for preparing the stain may have to be improvised with the same field sterilizer in which is immersed the glass flask or beaker containing the glycerin solution Temperature is controlled with a bath thermometer Excessive atmospheric humidity may cause fading of the stain on the thick drop This can be partially remedied by increasing the concentration of dilute stain

The thick drop examination affords at least a 20 1 time saving ratio over the thin smear Distortion of parasite morphology does occur in thick drop staining however and a knowledge of these variations is essential to correct diagnosis Once this knowledge is acquired examination of thick drops is easy and rarely does the thin smear have to be consulted for species confirmation

Ordinary medicinal mineral oil may be substituted for cedar oil for the immersion lens The 5× or 6× ocular lens is used initially and when a suspicious form is located more minute examination is done with the 10× ocular Examination of 50 oil immersion fields can be done in

two or three minutes by an experienced technician with nearly 100 per cent detection of clinical infections In survey work or where visceral malaria is suspected 100 fields are advised

New Aspects of Malaria. Conclusions derived from military experiences are presented by David R Talbot (M C U S N R) In areas of endemic malaria it should be a monthly routine to examine thick smears of blood from all military personnel on two successive days All persons with smears containing malarial parasites even those without symptoms should be treated vigorously to forestall attacks In general the policy of treating men for malaria only after they become infected is better than prophylactic treatment if adequate laboratory facilities are available This rule holds in peacetime or at any base where military urgency does not require a maximum number of men kept in the field to fight However in active combat areas especially where malaria caused by Plasmodium falciparum is endemic prophylactic measures must be adopted

Treatment with both quinine and atabrine is more effective in preventing recurrences than prolonged treatment with either alone Plasmochin may be indicated in rare specially selected cases of repeated occurrences As the result of some idiosyncrasy an occasional person is found whose infection does not respond to atabrine or quinine Treatment then must be given with the single effective drug

Diagnosis and treatment will be wrongly influenced if a positive Wassermann or Kahn reaction is considered pathognomonic for syphilis Malaria like syphilis is a protean disease and absence of chills and fever should not rule out its occurrence in people who are living or have lived in areas of endemic malaria

Tanret Reaction in Subtertian Malaria. The simple Tanret test for quinine in urine has been widely used to control administration and absorption of quinine during

(4) J A M A. 123 192 194 Sept. 25 1943

treatment of malaria From observations on European troops in a hyperendemic area of subtertian malaria J W Howie and R M Murray Lyon (R A M C) believe that properly used the test has even greater value than generally realized and may explain many apparent cases of quinine resistance

The reagent used is a combination of a solution of mercuric chloride 27 Gm dissolved by stirring in 1 500 cc boiling distilled water and a solution of potassium iodide 100 Gm dissolved in 500 cc cold distilled water The two solutions are mixed and 25 Gm glacial acetic acid is added The reagent keeps indefinitely

TECHNIC —The urine must be cold and clear to avoid false negatives Turbidity due to phosphates may be cleared with a few drops of dilute acetic acid other turbidities may be removed by filtration To about 10 cc urine a few drops of reagent is added If quinine is present in concentrations as low as 1 200 000 turbidity will appear which disappears on heating If turbidity persists on heating albumin is present which must be removed by precipitation with heat and acetic acid followed by filtration The albumin free filtrate should be cooled and retested Positive reactions are also found in urine of patients taking plasmochin but not of those taking other alkaloids in ordinary therapeutic doses

Every urine specimen passed by 100 consecutive men admitted with subtertian malaria during acute attacks and during convalescence was tested Treatment consisted of 30 gr quinine bisulfate daily for seven day after which the dose was reduced to 10 gr daily for three or four days and then to 5 gr daily before discharge Of the 100 soldiers 88 showed a positive Tanret reaction two to three hours after the first dose and continued to have strong reactions in all urine passed during the seven days on 30 gr daily All these men became fever free in 72 hours at most and recovered uneventfully Of the other 12 7 showed negative reactions in all urine until a dose of quinine was given intravenously when the reaction became positive and remained so even when the quinine was again given orally While the Tanret reaction remained

(5) Lancet 2 317 320 Sept 11 1943

negative they were all acutely ill recovery following the intravenous dose was rapid The other five showed occasional positive reactions at irregular intervals They were not dangerously ill and were not given quinine intravenously but recovery was slow pyrexia lasted five or six days and the Tanret reactions during convalescence were unsatisfactory

As controls 53 normal men were studied after taking 5 gr quinine orally Only 20 men showed positive reactions in an hour the others had positive reactions in one to five hours Reactions in five who were followed hourly were negative in 10 hours All were negative after 24 hours The authors believe that a negative Tanret reaction during presumably adequate quinine therapy indicates faulty quinine metabolism and that this condition may predispose to continuous infection which is recognized as favoring onset of blackwater fever It is therefore suggested that quinine administration and dosage in treatment and prophylaxis should be controlled *and adjusted for each individual by using the Tanret test*

Advances in Malaria Research are reviewed by Quentin M Geiman (Harvard Univ) Extensive studies with human malaria particularly induced malaria have proved *that patients acquire immunity during the course of an* infection Various investigations have helped to explain race susceptibility to malaria and development of immunity not to a species of plasmodium but to strains or races *of each species The immunity acquired is highly effective* against reinfection with the homologous strain but fails to protect against heterologous strains and species of parasites Discovery of different strains within a species helps to explain resistance or tolerance of a given population to local strains the length of time required for effective immunity to develop susceptibility to foreign strains variable clinical activity observed for different strains of the same species and variable response to antimalarial drugs

(6) New England J Med 229 324 332 Aug 19 1943

Two approaches have been used to elaborate the mechanism involved in natural and acquired immunity Cellular reactions to various types of malaria have been studied and standard immunologic methods used in investigating humoral response to infection Defense against infection depends on response of the lymphoid macrophage system Phagocytosis occurs primarily in the spleen with decreasing activity in liver and bone marrow Natural immunity is demonstrated during early days of the infection by a relatively small amount of phagocytosis During and after the crisis phagocytic activity is greatly increased and associated with proliferation of macrophages This initial response requires time for mobilization in non immune animals but response after superinfection is rapid in animals with acquired immunity Proliferation of lymphoid macrophage tissue in the spleen offers a basis for splenomegaly or progressive increase in size of the spleen during the disease This cellular defense is active only against the strain or race of parasite that caused the infection Greater susceptibility of children to malaria indicates either that more time is necessary to acquire effective immunity or that the defense mechanism is less efficient than in adults

Immunologic studies have demonstrated protective antibodies in malaria but serologic tests have not been clinically practicable The studies demonstrate the slow but gradual increase in development of acquired immunity When the course of the infection is interrupted by immediate treatment formation of antibodies is prevented and hence no immunity is acquired Here is the basis for the frequent observation in a native population that a seasoning process to malarial paroxysms is necessary before beginning treatment Assuming variation of specific antigenicity and host response under extreme conditions of climate and malnutrition the level of immunity or activation of the lymphoid macrophage system and production of protective antibodies is entirely dependent on intensity and duration of infection Short

lived infections produce little or no immunity In long standing chronic infections a high grade of immunity is acquired

The ideal drug for malaria therapy has not been found and there is no general agreement about treatment This might be expected in view of the great variety of parasitic strains wide difference between benign tertian and malignant tertian malaria and additional effects of race susceptibility acquired immunity malnutrition and other factors Three antimalarial drugs have been tested and used successfully the cinchona alkaloids of which quinine is best known and the synthetics atabrine and plasmochin Atabrine is the only substitute for quinine because plasmochin is useful only for specific destruction of gametocytes or sexual stages of malignant tertian malaria that lead to infection of anopheline mosquitoes and transmission of the disease

Analysis of the serious potentialities reveals that the following factors will play a role in spread of tropical diseases including malaria from returning troops time of year when troops return presence of necessary vectors *for transmission type of sanitation in rural or urban* communities to which men return and occupation assumed by the returned soldier The first three are most important Malignant tertian malaria is seldom found in regions having an average summer temperature lower than 70 F and an average winter temperature lower than 48 F If infection is brought into such areas small epidemics may occur but eventually the disease dies out Consequently the major problem with returning troops is to recognize and make an accurate and speedy diagnosis of malaria Since there is no need for these men to acquire immunity a radical cure should be the aim of treatment

Drug Treatment of Malaria, Suppressive and Clinical, is discussed in Circular Letter No 153 Office of the Surgeon General of the Army [7] Available evidence in

(7) J A M A 123 205 208 Sept. 25 1943

dicates that atabrine is as effective as quinine (or more so) both in suppressive use and in treatment of clinical attacks Plasma level of the drug used is fundamental in determining its efficacy Generally the rates of absorp tion of quinine and atabrine are not significantly different Quinine is localized in the tissues to a smaller extent than atabrine and effective plasma concentrations therefore are usually attained shortly after beginning its adminis tration Atabrine however at first is taken up to a much larger extent by the tissues so that effective plasma concentrations are reached later To attain effective plasma concentrations of atabrine it is necessary to give relatively large initial doses or to wait for a varying period while the drug accumulates

Plasmochin cannot be used for suppressive treatment since in safe doses it has little effect on schizonts For the same reason it fails to control clinical attacks of malaria hence plasmochin alone cannot be used This drug has some degree of special action in destruction of gametocytes an effect which does not influence the course but which might be of value in controlling spread of the disease

Each of these drugs is capable of producing toxic reactions Occasional individuals are peculiarly intolerant of each

Drug suppressive treatment is an emergency procedure which should be used only when troops must accomplish a mission in an area where there is a substantial risk from malaria and where mosquito control is not possible There is no drug known which in safe doses will pre vent mosquito borne infection with malaria However atabrine taken regularly in proper doses suppresses clinical symptoms for varying periods and enables men to remain active despite infection which otherwise would incapacitate them For suppressive treatment to be effective the drug must be taken regularly The recommended method is to give 0 1 Gm atabrine once daily at the evening meal six days each week An alternative method which has been

satisfactory in some areas is to give 0 05 Gm atabrine once daily at the evening meal six days each week and 0 1 Gm atabrine at the evening meal on the seventh day Quinine should not be used for suppressive treatment except in cases of severe intolerance to atabrine Recommended dosage is 0 6 Gm quinine sulfate daily at the evening meal *Plasmochin should not be used for suppressive* treatment at any time

Atabrine alone is the treatment of choice for clinical attacks of malaria It should be given in relatively large initial doses followed by smaller maintenance doses Recommended dosage is atabrine hydrochloride 0 2 Gm and sodium bicarbonate *1* Gm by mouth with *200–300* cc water (or an equal amount of sweetened tea or fruit juice) every six hours for five doses followed by 0 1 Gm three times daily after meals for six days (total 2 8 Gm in seven days) If atabrine is not available quinine alone should be used quinine sulfate 1 Gm by mouth three times daily after meals for two days followed by 0 6 Gm three times a day after meals for five days (total 16 Gm in seven days)

Plasmochin may be given in connection with either of the foregoing treatments however its routine use is not advised If plasmochin is given the patient must be hospitalized and closely observed Dosage given below must not be exceeded Plasmochin may be given immediately following atabrine (not with it) or along with quinine on the last days of treatment with that drug The course consists of plasmochin 0 01 Gm by mouth three times daily after meals for four days except for debilitated patients who should receive only two doses a day Each dose of plasmochin should be accompanied by at least 1 Gm sodium bicarbonate Fluid and sugar intake should be liberal during and for some days after the course Plasmochin should be discontinued immediately if toxic symptoms appear

In cases of severe malaria or malaria complicated by vomiting coma or other serious disorders and whenever

a patient cannot retain or fails to respond to oral medica tion atabrine or quinine should be given parenterally Recommended parenteral methods follow (1) Atabrine dihydrochloride 0 2 Gm in 5 cc sterile distilled water is injected intramuscularly into each buttock (total 0 4 Gm) If necessary, one or two additional doses of 0 2 Gm may be given intramuscularly at six to eight hour intervals As soon as the patient can take and retain oral medication atabrine should be given by mouth in such doses as to give a total by both routes together of 1 Gm in 48 hours followed by 0 1 Gm three times a day after meals for five days (total 2 8 Gm in seven days) (2) Quinine di hydrochloride 0 6 Gm in sterile isotonic solution of sodium chloride 300–400 cc (minimum 200 cc.) is injected slowly intravenously This may be repeated in six to eight hours if necessary When the patient can take and retain oral medication a complete course of atabrine (preferable) or quinine should be given as already described

Malaria. The standard routine of specific treatment as recommended by Australian Army authorities con sists of four courses one after the other (1) 10 gr quinine sulfate three times daily for three days (2) 0 1 Gm atabrine three times daily for five days (3) 0 01 Gm plasmochin and 5 gr quinine sulfate three times daily for five days (4) 0 1 Gm atabrine six days each week for six weeks

The quinine should be in solution and the following prescription is advised

Quinine sulfate	10 gr
Dilute sulfuric acid	10 minims
Simple syrup	1 drachm
Chloroform water q s ad. ½ fluidounce	

The sulfuric acid renders the quinine sulfate soluble The same result can be achieved by using quinine bisul fate directly but the equivalent dose of this is 25 per cent higher e g 12½ gr bisulfate as compared with 10 gr sulfate The quinine must be given in solution even if the drug is supplied in the form of tablets

(8) M J A stral pp 2 pp 81 84 A g 7 1943

Because it may irritate the gastro intestinal tract atabrine is given after meals with water Plasmochin is given similarly to prevent sudden absorption for the margin of safety between therapeutic and toxic doses is small Quinine is given initially because it acts more quickly on the schizonts than does atabrine but to conserve quinine atabrine is given after three days

Actions of the three antimalarial drugs may be summarized as follows (1) quinine acts on an asexual form (probably schizonts and merozoites) of all three malarial species and on the gametocytes of Plasmodium vivax and malariae (2) atabrine has essentially the same actions (3) plasmochin acts on an asexual form of Plasmodium vivax and malariae it is effective against the gametocytes of all three forms Atabrine and plasmochin are never given concurrently because of a reciprocal accentuation of toxic effects

Treatment of Malaria. E T Brennan (Sydney) reviews the effect of antimalarial drugs on benign tertian and subtertian malaria and treatment routines recommended in the United States and in the British Army In all parts of the world schemes of treatment are gradually becoming more uniform awaiting a new and better antimalarial drug

Standard treatment of malaria in Australia is administration of 10 gr quinine sulfate three times a day for three days followed by 0 1 Gm atabrine three times a day after food for five days followed by 0 01 Gm plasmochin three *times a day after food and 5 gr quinine sulfate three* times a day after food for five days If more convenient quinine can be given in a single dose at night The course of plasmochin and quinine treatment may be reduced from five to three days in uncontrolled areas of hyperendemic malaria and where for military reasons it is necessary to shorten the course of treatment After conclusion of the standard therapeutic course every patient

(9) M J A st alia 1 189 193 Ma 4 1944

should be continued on a schedule of 1 tablet of ata brine (0 1 Gm) six days each week for six weeks

In addition to all important specific drug treatment a *few points in general treatment are significant* (1) diet should be light while temperature is raised and before a paroxysm is due (2) hot lemon drinks and aspirin during the shivering stage to relieve severe headache (3) change of pajamas and bedding after sweats (4) plenty of liquids (5) rest in bed during febrile period but not for the whole duration of treatment Malaria patients in their first few attacks tend to be sorry for themselves so to keep them in bed after fever is controlled is likely to render them introspective and morbid

During convalescence iron and arsenic tonics are neces sary Large doses of saccharated ferrous carbonate with pooled A B C and D vitamins are useful for the anemia Novarsenobillon (0 6 Gm) given intravenously is useful in chronic malarial debility especially that associated with chronic benign tertian malaria

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MENINGOCOCCIC INFECTIONS AND MENINGITIS

Meningococcic Infection in Soldiers Worth B Daniels Sydney Solomon and William A Jaquette Jr (Fort Bragg N C) state that infection with the meningococcus arises in *the nasopharynx and invades the blood stream* with localization in the skin joints meninges and other body tissues Meningitis is the most dramatic phase of this form of septicemia Diagnosis in the phase of septicemia can and must be made on clinical grounds and prompt therapy instituted to prevent advent of meningitis The authors *observed 80 soldiers with meningitis (78 treated* with sulfadiazine and 2 with sulfapyridine) and 32 with meningococcemia (all treated with sulfadiazine) with one death in the former group The usual initial dose in the cases of meningococcemia was 4 Gm followed by 1 Gm.

(1) J A M. A 123 1 9 S pt 4 1943

every four hours until the temperature remained normal for two days Parenteral administration was used when patients were vomiting The optimal dose of sulfadiazine in meningococcic meningitis has not yet been determined but the authors experience indicates that it is probably lower than that in general use Confirmation of the diagnosis by serologic methods was attempted in 71 cases 49 of meningitis and 22 of meningococcemia In 31 of the former and 17 of the latter there were increases in titer of twofold to eightfold In this group four cases of meningitis and nine of meningococcemia were not confirmed bacteriologically In only 2 of the 22 cases of meningococcemia was there neither bacteriologic nor serologic confirmation Nineteen of the 23 cases with no increase in agglutinin titer were confirmed bacteriologically

Lewis Webb Hill and Haseltine Smith Lever[2] (Camp Edwards Mass) report 68 cases 13 of meningococcemia only without meningitis Of 62 cases in which spinal puncture was done spinal fluid was clear in 31 Organisms were frequently recovered from clear fluids Positive blood cultures were obtained in 40 cases In 11 undoubted cases the organism could not be recovered either from blood or spinal fluid These patients were treated with sulfadiazine administered intravenously during the first 24 hours Five Gm sodium sulfadiazine in 100 cc distilled water intravenously was followed by 1 000 cc of 5 per cent dextrose in isotonic sodium chloride solution Eight hours later 2 5 Gm sodium sulfadiazine was given intravenously followed by 1 000 cc of 5 per cent dextrose solution This was repeated eight hours later In cases of stupor or in presence of nausea or vomiting intravenous therapy should be continued every eight hours If progress was satisfactory 1 5 Gm. was given orally eight hours after the last intravenous dose and repeated every four hours Then 1 5 Gm was given every *six hours two days after temperature receded* Optimal blood concentration is not known but the authors believe it should not fall below 8 mg per 100 cc Twenty

(2) J A. M A 1 3 9 1 3 S pt 4 1943

three patients had reactions to sulfadiazine which were not serious and of short duration When there was macroscopic hematuria sulfanilamide was substituted In 68 cases in this series there were no deaths

Hill and Lever state that it is possible to diagnose early meningococcic infection with reasonable accuracy in a high proportion of cases by clinical means alone The four cardinal signs and symptoms are headache vomiting chill and rash Early treatment is of utmost importance and should be begun without waiting for bacteriologic diagnosis

[The first clear demonstration that meningococcic infections may occur with septicemia but without meningitis was made by W W Herrick in World War I —Ed.]

Use of Chemotherapy in Case of Tuberculous Meningitis is reported by H M Keith

Boy 2 was admitted with clinical signs of meningitis consisting of moderate lymphocytosis in the spinal fluid increased globulin content and presence of four acid fast bacilli on a fluid smear Promizole (4,2 diaminophenyl 5 thiazole sulfone) was begun the day of admission and 15 gr was administered in the first 24 hours The dose was increased by 5 gr daily to a maximum of 50 gr Concentration of hemoglobin red and white blood cell counts and blood smears were studied daily Clinical progress was good and at the end of two weeks there were no clinical signs of meningitis Lumbar puncture revealed clear spinal fluid containing 0 2 mg promizole per 100 cc Acid fast bacilli were not found by either auramine or Ziehl Neelsen stain

That clinical improvement followed administration of the sulfone is only suggestive but the drug has been shown to have good effect on tuberculous lesions in guinea pigs Acceptable proof of tuberculous infection by production of the disease in an animal inoculated with spinal fluid from the patient was not established Therefore evidence of tuberculosis while clinically convincing must be considered presumptive

(3) P oc. St ff M t. M y Cl n. 19 36 37 J n 26 1944

POLIOMYELITIS

Vitamin B_1-Deficient Animals and Poliomyelitis John A Toomey William O Frohring and William S Takacs[4] (Western Reserve Univ) report unsuccessful attempts to acclimate the Flexner M V strain of poliomyelitis virus to white rats by making them deficient in vitamin B_1 or by overfeeding them with vitamin B_1 When white mice were the test animals and the Lansing poliomyelitis virus (cotton rat strain) was the test inoculum there were more obvious paralytics in a vitamin B_1 overfed group than in a vitamin B_1 deficient group in the first transfer generation When a second transfer generation was made with cords of mice that died without paralysis in the first generation there was no significant difference in total number of animals *paralyzed in the overfed and the deficient groups*

Paralysis developed more quickly in normally fed white mice than in animals fed a diet deficient in vitamin B_1 and in those given a supplemental dose of the vitamin This point was not conclusive however since some animals *of the deficient group that died during the incubation period* of paralysis might also have carried the virus

Serologic Relationships in Poliomyelitis Group of Viruses were studied experimentally by Claus W Jungeblut[5] (Columbia Univ) Cross neutralization tests between two mouse adapted strains of human poliomyelitis virus and Theiler s virus of mouse encephalomyelitis and corresponding antiviral immune serums revealed overlapping reactions of various degrees among the three viruses In some instances these reactions were reciprocal in others nonreciprocal Different results were obtained with intracerebral and intraperitoneal methods of testing the former gave evidence of group-specific and the latter of strain specific virus inactivation

It seems reasonable to assume presence in the virus

(4) Yale J Biol & Med 16 477-485 May 1944
(5) Am J Pub Health 34 259 264 March 1944

molecule of components with varying degrees of specialization associated with virus multiplication and with virus invasion by peripheral channels There is evidence to show that the peripherally acting component can deteriorate and become silent in the pathogenic sense

Available data mark the two murine strains (Sk MM) as separate but closely related viruses in which homologous antigens are blended with heterologous antigens Both viruses have incorporated in them certain accessory fractions peculiar to simian poliomyelitis virus and to Theiler s virus This leads to an impression that human poliomyelitis virus and Theiler s virus may be natural variants of a common viral root whereas the experimentally adapted murine viruses represent hybrid strains which occupy a position somewhere between these two fixed borders Inclusion of these several viruses in one family of intrinsically related viral agents designated as the poliomyelitis group appears justified in the light of this antigenic analysis

New Developments in Infantile Paralysis are reviewed by Don W Gudakunst (Nat l Foundation for Infantile Paralysis Inc) Many clinicians believe that poliomyelitis primarily if not almost exclusively affects the anterior horn cells of the spinal cord producing its symptoms by death of these cells or by damage from edema and hemorrhage into the adjacent cord Undoubtedly the name acute anterior poliomyelitis has tended to further these misconceptions of a sharply limited pathology Careful studies of hundreds of animals infected by routes other than direct intracerebral inoculation show that the cord may or may not be involved while the brain always is A similar condition has been found in a few human patients who died of intercurrent causes either in a mild infection or before there had been time for extensive spread The anterior gray part may or may not be involved when lesions are present in the cord The posterior columns pyramidal tracts lateral and intermediate zone or internuncial cells intervertebral ganglions or dorsal roots may show unmis

(6) N w York St t J Med 43 1514 1517 A g 15 1943

takable signs of virus invasion and damage with no correlation between the severity or extent of lesions in these areas and that of lesions in the anterior horn cells

In all diagnosable cases of poliomyelitis with the possible exception of early nonparalytic types with complete spontaneous arrest of symptoms there is encephalitis with involvement of parts of the motor cortex There is commonly an accompanying meningitis usually mild and probably secondary to the deeper involvement This may or may not be accompanied by clinical symptoms and there may or may not be further pathologic changes in the cord Medulla midbrain and thalamus are routinely involved in both the experimental animal infected by the gastro-intestinal or pharyngeal routes and in man as evidenced by study of pathologic changes and by recovery of the virus These may be the only areas that show such changes

Interpretation of clinical symptoms on the basis of pathologic findings is not easy Examination of autopsy material commonly reveals extensive pathologic changes totally unsuspected and unpredicted by clinical symptoms alone Likewise clinical manifestations at times are apparently out of all proportion to the severity of the manifest lesions in the anterior horn cells of the corresponding cord segment Thus the picture is complicated With extensive involvement of both sensory and motor cells over large areas of the central nervous system and with the changes varying from slight reversible reactions to complete destruction of many cells it is to be expected that there would not be a single clinical picture It is certain that the simple concept of paralysis as the sole or main symptom is no longer reasonable That paralysis can and does occur is certain but it is equally certain that it is an inconstant part of a complicated train of symptoms With such massive and extensive involvement it is apparent that pain hyperirritability increased muscle reaction to stretch reflex (sometimes referred to as spasm) and in-co-ordination of muscle action could be expected It is also apparent

that inability to perform voluntary motion of a muscle could be due to many neural mechanisms other than death of anterior horn cells Disturbances at many levels in physical continuity and function of motor pathways with changes in nuclei and in communicating and connecting tracts of the central nervous system could well cause a pseudo- or temporary paralysis without significant damage in the corresponding anterior horn cells It is not necessary to hypothecate ephemeral changes in anterior horn cells when demonstrable lesions occur at other key points of the neuromuscular system

From this it is apparent that there is a need for some change in the system of therapy aimed at securing rest of damaged anterior horn cells through lessening of motion of the extremity and at providing protection of a weakened muscle from the pull of a strong unaffected opposing muscle with the hope of preventing future contractures and fibrotic changes

There is no real evidence that either of these objectives was accomplished in most cases Certainly there is no physiologic evidence that muscular rest alters the rate of degeneration of infected or damaged anterior horn cells nor is there satisfactory evidence that protracted immobilization prevents contractures and deformities

Kenny s method of treatment is based on a concept of poliomyelitis that differs from that of flaccid paralysis as the predominant symptom To her spasm or increase in tonus and irritability of voluntary muscle is the important symptom This does not preclude the possibility of true paralysis resulting from massive destruction of anterior horn cells but according to her observations this is present in not over 10–15 per cent of patients admitted to any hospital for early medical care In the usual case spasm is directly or indirectly responsible for most of the symptoms The early pain and later tenderness on pressure and action and still later contractures are due to this spasm Furthermore inability of a certain muscle to contract and to produce useful motion may be due to pull of the opposing

muscle or muscle groups acting as a simple brake or to the fact that the muscle is pulled out of its normal resting stage into an extended position from which it is not capable of producing a contraction Much that has been called paralysis and was thought to be due to anterior horn cell damage is according to Kenny not flaccid paralysis but spasm in the opposing muscle due probably to lesions at some level higher than the anterior horn cells or to other changes in neuromuscular structure and function

Kenny s treatment for these conditions is aimed first at overcoming pain and spasm and second at providing early muscle training to re establish muscle function and motor pathways Both objectives involve technics that have tended to set this special treatment aside as a method Actually there is little that is new or different in the modalities employed The method of application time of application and particularly their purposes are different

Application of heat by use of compresses at unusually high temperatures quickly relieves the common symptom of pain found early in many severe poliomyelitis infections Evidences of disturbances of circulation and changes in *temperature of the involved parts rapidly disappear* There are beneficent effects in addition to the primary purpose of providing relaxation of spasm by reflex action

As soon as pain and tenderness subside and motion can be performed without discomfort the affected parts are moved through their utilizable arc of motion The aim is not that of restoring strength but rather of securing rhythm and co ordinated action of all muscles concerned with any motion Weakened in co ordinated or alienated muscles (Kenny s terms) are stimulated and directed by individual attention to resume their correct function normal in point of time and direction of action Other muscles not involved or involved to a lesser degree are discouraged from assuming any *abnormal action as the result of the* patient s wilful or unconscious effort to effect a desired motion

As a result of the combination of heat regulated exer

cise direction of motor impulses and absence of long periods of immobilization patients under the Kenny treatment show many desirable benefits There is much that is not fully understood about this or other methods of treatment and much must be done to lessen the time and amount of work now required to apply successfully the Kenny method to any large group of patients While there is a lack of *scientifically controlled evidence both with respect to* clinical cases and as collected in the laboratory few will deny that Kenny has made a great contribution to control of the end results of poliomyelitis

Effect of Vitamin B_1 Deficiency and of Restricted Food Intake on Response of Mice to the Lansing Strain of Poliomyelitis Virus Claire Foster James H Jones Werner Henle and Frieda Dorfman (Philadelphia) observe that in several experiments a deficiency of vitamin B_1 in the diet increased the resistance of mice to the Lansing strain of poliomyelitis The source of the virus was a suspension of infected mouse brain in saline which was injected intracerebrally Both mortality rate and incidence of paralysis were lower in deficient animals than in normally fed controls Protection was more pronounced with respect to paralysis than with respect to the number of deaths Some deaths in the deficient groups were undoubtedly due to the vitamin deficiency as indicated by numerous deaths among groups of animals on the deficient diet but given injections of a suspension of normal brain An attempt was made to maintain a state of chronic vitamin deficiency by giving small amounts of the vitamin The results also seem to indicate that the effect of the deficiency was more in delaying the action of the virus than in preventing its action The greatest difference between normally fed and deficient animals receiving the virus came at about the twelfth day after inoculation

Comparable results were obtained by restricting intake of the complete diet to 1 Gm per mouse per day (about 40 per cent of the intake of normally fed mice) Restric

(7) J Expe Med 79 2 1 34 F bru ry 1944

tion of caloric intake alone gave similar results Restriction of food intake was effective in experiments in which extra vitamin B_1 was given in the diet and also when a diluted saline solution was given by stomach tube to assure sufficient intake of fluid.

Other data are necessary before an explanation can be given for the manner in which these deficiencies increase resistance of the mice to the virus of poliomyelitis

Degree, Extent and Mechanism of Muscle Spasm in Infantile Paralysis Using electrical methods to determine action currents Harry D Bouman and R Plato Schwartz (Univ of Rochester) found that spasticity is present in infantile paralysis but the question is whether this is actually responsible for weakening the muscle or whether it is merely another consequence of the disease Spasticity is a property of the antagonist of the weakened muscle but *is found also in muscles whose antagonists do not show* evidence of weakening Neck muscles show spasticity in nearly all cases Spasticity is found also in weakened muscles Often spasticity in weakened muscle is actually stronger than the maximal voluntary contraction the patient can perform This evidence indicates that spasticity is a general phenomenon in early stages of infantile paralysis In complete paralysis i e when there is no evidence of action currents from stimulation by voluntary effort or stretch reflex there is no spasticity

Evidence indicates that spasticity is a reflex phenomenon and is not due to a process localized in the muscle itself such as fibrillation or inflammation A muscle deprived of its nerve supply may show fibrillation but when no voluntary or reflex contraction of muscle could be obtained spasticity also was absent When action currents are recorded simultaneously from four muscles spasticity spreads to both the ipsilateral antagonist and to both the homolateral muscles This can be explained only if spasticity is a reflex phenomenon

According to Sherrington s principle of reciprocal in

(8) New York State J Med 44 147 153 Jan 15 1944

nervation contraction of a muscle should result in relaxa tion of the antagonist and not as in infantile paralysis in contraction (spasticity) This reversal of reciprocal innervation is important in maintenance of spasticity in poliomyelitis The mechanism then is a vicious circle in which one muscle keeps its antagonist going and the antagonist in turn maintains spasticity in the original muscle Only when spasticity has disappeared or when one of the two muscles is completely paralyzed so that it can no longer produce spasticity is this vicious circle broken

Evidently the mechanism in poliomyelitis is different from that which underlies spasticity in spastic paralysis caused by a transverse cord lesion in infantile paralysis it might be supposed that the lesion is much closer to motor neurons of involved muscles Inhibitory impulses from higher centers apparently are blocked close to motor neurons either at the synapses of these fibers at the motor neurons or because of failure to conduct in internuncial cells inserted in fibers coming from higher centers This must mean that some motor neurons are no longer able to receive impulses from higher centers either inhibitory or excitatory while they are still able to receive impulses from short reflex arcs In that case only the inhibitory impulses fail to affect the motor neuron while both short reflex arcs and voluntary impulses are still effective Thus spasm of the particular type encountered in poliomyelitis can be explained owing to a decrease in excitability of motor neurons

That spasticity is independent of muscle weakening and appears in agonist and antagonist muscles which do not show weakening means that spasticity in a certain muscle is not automatically followed by weakening of its antago nist In fact spasticity and weakening are two separate phenomena each dependent on disturbance of specific functions of the anterior horn cells

Poliomyelitis in British and American Troops in the Middle East. John R Paul W P Havens Jr (M C

A U S) and C E Van Rooyen[9] (R A M C) attempted isolation of poliomyelitis virus from the stools of patients with typical and borderline cases of poliomyelitis seen during 1943 among British and American troops in Libya Egypt and Palestine The tests were done to determine their local value as confirmatory diagnostic procedures and to determine whether adults with such cases which occurred mostly sporadically harbor the virus in the intestinal tract in the same manner as do juvenile patients in areas where the disease is more apt to be epidemic

The stools or colon contents in 9 of 15 cases were positive for poliomyelitis all of these positive cases were fatal In 1 of the 15 cases the result was unsatisfactory because of premature death of the monkey These results suggest that the amount of virus present in the intestinal tract was greater in the more severe than in the milder cases Another point to be emphasized is that most of the stools were collected in the fatal cases (mostly fulminating in type) earlier in the disease on the third to tenth day than in the other poliomyelitis cases It is known that the chances of obtaining positive results are greater during the first than during the later weeks of the disease All tests for virus in the stools from cases other than typical poliomyelitis (polio encephalitis acute benign lymphocytic meningitis and localized neuritis with diarrhea and fever) were negative Several of the monkeys developed fever without symptoms of myelitis and were killed Histologic examination of the spinal cord was negative and no doubtful positive results were obtained However failure to find poliomyelitis virus in such cases does not necessarily exclude the disease.

(9) Brit M J 1 841 843 June 24 1944

RABIES

Prevention of Experimental Rabies Howard J Shaughnessy and Joseph Zichis (Illinois Dept of Pub Health) report results obtained in treatment of wounds contaminated by rabies virus using fuming nitric acid soap solution sulfanilamide or tincture of iodine When treatment was instituted in 30 minutes only 11 per cent of those treated with fuming nitric acid and 6 per cent of those treated with soap solution became infected compared with about 63 per cent of the untreated control animals Application of treatment in two hours was apparently somewhat less effective and application in six hours was definitely le s effective than when it was applied in 30 minutes

In a limited number of guinea pigs the results of apply ing tincture of iodine in 30 minutes compared favorably with results obtained with either fuming nitric acid or soap solution However used after an interval of two hours it appeared to be considerably less effective than the other substances

Packing the wounds with sulfanilamide after treatment with soap solution seemed to have no effect on the incidence of rabies

The results of these experiments show that in treatment of guinea pig wounds inoculated with fixed rabies virus irrigation with 20 per cent solution of soft soap is as effec tive as chemical cauterization with fuming nitric acid and possibly more effective

[This is an important contribution as the use of soap solution should be much more conducive to healing with minimal deformity than is the use of fuming nitric acid which has been thought better than other substances —Ed]

(6) J A. M A. 123 528 533 Oct. 30 1943

RHEUMATISM AND RHEUMATIC FEVER

Palindromic Rheumatism, a new form recently described by Hench and Rosenberg is characterized by frequent attacks of acute arthritis periarthritis and occasional para arthritis with severe pain considerable disability swelling and redness about the joint Attacks appear suddenly and develop rapidly lasting a few hours to days without leaving residual symptoms or physical findings Many cases include para arthritis consisting of firm tender red swellings on the skin generally associated with attacks of arthritis These swellings also appear suddenly and disappear in a short time The cause of this condition is still obscure Allergic and infectious factors have been postulated but not proved Evidence points away from an allergic basis That psychogenic factors may play a role has been suggested The natural course of the disease tends to be long but without permanent crippling No form of therapy has proved of definite value although cinchophen has been reported to give relief William D Paul and William P Logan (State Univ of Iowa) report a case

Woman 49 had arthritic attacks with symptoms of para arthritis She estimated that she had had at least 100 severe and several hundred minor attacks and onset often followed periods when she became nervous or angry She believed that eating eggs might also have had some part in initiating attacks *although this was doubtful Cinchophen as oxyliodide* with physical therapy and active motion in the joints appeared to help

Role of Central Factors in Pathogenesis of Rheumatic Disorders Ralph Pemberton and C Wesler Scull (Abington Pa) present a survey of the clinical patterns of rheumatic disease which reveals that the disorder not only affects the anatomy of articular structures but also involves the functional integrity of the nervous respiratory neurovascular muscular *and gastro intestinal systems* The blood also presents abnormalities of cellular and fluid

(1) J Iowa M Soc. 34 101 10 M ch 1944
(2) Ann Int Med 19 482-495 S ptember 1943

components Etiologic and sustaining factors including infectious traumatic and nutritive influences are varied and numerous Susceptibility to rheumatic disease is greater in certain families than in others and varies with body build These several facts may be correlated by considering the symptoms of rheumatic diseases at least rheumatoid (atrophic) and osteo- (hypertrophic) arthritis as primarily direct consequences of disturbance in the several functions of the neuro-endocrine system as a whole and especially in those of the pituitary gland These disturbances of the pituitary may be determined by congenital inadequacy or by excessive stimulation with subsequent periods of functional hyper or hypo-activity It appears unlikely that any single factor is responsible for producing the full pattern in any case

Influence of the pituitary is perhaps most clearly operative in so called menopausal arthritis Exacerbation of stiffness and pain in an arthritic during the premenstrual phase of the reproductive cycle and remission of rheumatic complaints during pregnancy although more immediately referable to gonadal activities also involve pituitary activities Similarly arthralgic manifestations associated with hypothyroidism may involve pituitary factors The fatigue and general asthenia characterizing many cases of chronic arthritis could be attributed to adrenocortical insufficiency secondary to pituitary dysfunction Circulatory and thermoregulatory disturbances seen in many arthritics and involving imbalance of the nervous system may likewise depend on endocrine influences initiated in the pituitary organ Certain skeletal and cartilaginous defects characterizing rheumatic diseases are seen in cases of frank endocrine disease and some have been produced by pituitary substances in experimental animals

These considerations in addition to their theoretical interest in accounting for the symmetrical distribution of lesions and certain systemic dysfunctions bear suggestive therapeutic corollaries which have not yet been fully explored and which invite clinical as well as experimental

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(1) J Iowa M Soc. 34 101 10 March 1944
(2) Ann. Int. Med. 19 482-495 September 1943

doses of sodium salicylate physical signs of heart disease developed The observations suggest that a plasma salicy late level of at least 350 gammas per cc may be required to suppress the rheumatic reaction and that plasma levels below 200 gammas per cc may be sufficient to relieve symptoms while masking a progressive inflammatory process

Coburn emphasizes that salicylic acid is not the final solution to therapeutic problems in rheumatic fever Other drugs may be found more effective in suppressing the rheumatic reaction but like salicylic acid these too may not modify the duration of rheumatic activity To effect this one of two objectives must be realized Either the immune response of the host must be modified so that the patient recovers promptly after a monocyclic attack or the capacity of the infecting micro organism to elaborate antigen must be inhibited by a chemotherapeutic agent At present therapy is limited to suppression of the inflam matory process and a high concentration of salicylate in the plasma appears effective for this purpose This concen tration is controlled by absorption degradation possible localization in tissues and excretion of the drug the exact role of each of these four factors in controlling plasma level remains to be determined

Management of Navy Personnel with Rheumatic Fever Alvin F Coburn reports on 73 patients 65 acutely ill with rheumatic fever and 8 with quiescent rheumatic heart disease All but one were under 30 and half were under 21 Seven patients had a familial history of rheu matic fever Eight had had rheumatic fever during child hood and six had experienced growing pains or severe epistaxis suggesting subclinical rheumatic activity Five had severe rheumatic heart disease prior to enlistment Fourteen had contracted frequent sore throats and 36 had had tonsillectomies during childhood Most of the patients came from rural districts Types of attacks were similar to those seen in young adults in civilian hospitals Pain

(5) U S N M B ll. 41 13 4 1328 S pt mbe 1943

venous administration of sodium salicylate is required to obtain a rapid rise in plasma concentration of salicylate to 400 gammas per cc or higher A therapeutic technic for the use first of intravenous and, later oral salicylate is suggested for rapid development and maintenance of plasma salicylate levels above 350 gammas

TREATMENT —*Day 1* 10 Gm sodium salicylate in 1 000 cc of 0 9 per cent sodium chloride is administered by intravenous drip in four to six hours *Day 2* If the patient has any rheumatic symptoms or if the temperature has not reached normal 20 Gm sodium salicylate is administered in 2 000 cc of 0 9 per cent sodium chloride in eight hours *Day 3* The preceding dose may be repeated if necessary but with the patient symptom free and afebrile 10 Gm sodium salicylate is adequate *Days 4–6* Sodium salicylate infusions are continued daily until the blood sedimentation rate has made an appreciable drop e g about 20 per cent *Days 7–30* Oral therapy replaces intravenous treatment Doses of 1 6 Gm sodium salicylate and 0 6 Gm sodium bicarbonate are administered every four hours day and night A total of 10 Gm. sodium salicylate is given daily during this period *Day 30* After two weeks or more in which sedimentation rates remain within normal limits the patient is allowed a trial week at bed rest without any salicylate If he remains symptom free and maintains a normal sedimentation rate for one week he is allowed up progressively If however frank symptoms fever or a marked rise in blood sedimentation rate appear during this test week another two week course of therapy is indicated This course is begun with oral medication or with one intravenous infusion of 10 Gm followed by oral dos s

Frequent study of sedimentation rate is essential for guiding this course of treatment and occasional plasma salicylic acid determinations are also useful This check led to discovery that one patient was discarding the drug and that another was receiving twice the dose ordered Furthermore there may be occasional patients who excrete the drug rapidly conjugate it abnormally or fail to absorb it properly

Two years experience with this technic shows that in none of 38 rheumatic patients treated with 10 Gm sodium salicylate daily did valvular heart disease develop and that in 21 of 63 similar patients who received only small

SMALLPOX

Differential Diagnosis of Chickenpox and Smallpox. Although these two diseases are well differentiated cases of mild smallpox and severe chickenpox may offer some difficulty in diagnosis Conrad Wesselhoeft (Harvard Univ) reviews characteristic signs and symptoms of both diseases The incubation period of chickenpox is 13–20 days the average for smallpox is 12 days but it may vary from 8 to 21 days In general prodromal symptoms are absent or slight in chickenpox and severe in smallpox

The course of chickenpox is usually two or three days of fever accompanying eruption of vesicles which continues two to five days The scabs may come off in a week but often they cling to a tough central root for two weeks or longer During the scab stage the patient is up and about The protracted course in smallpox consists of severe and prolonged prodromes followed by a brief period of lowered temperature and relative comfort First signs of the eruption then appear usually during the third or fourth day of acute illness but sometimes as late as the seventh day In general all lesions come out together and thus tend to be at the same stage Frequently however lesions appear on the face 24 hours earlier than elsewhere and sometimes in a given area one may find lesions in different stages of development However as a rule there is much wider variation in the lesions of chickenpox Smallpox lesions begin as macules that last 24 hours After this there may be another 24 hours in which they have a shotty feel Then come firm walled umbilicated vesicles that become opaque pustules in 24–72 hours Fever which has been slowly mounting through the vesicular stage rises abruptly with the pustular stage Pustules remain four to six days and then turn into crusts and scabs These often remain a week or two and as they come off they leave red pits that become white pitted scars after

(7) New E gl d J Med 230 15 19 J n 6 1944

in a joint of the lower extremity was the initial symptom in the majority and onset was usually precipitous often occurring while the patient was at rest

TREATMENT—Objectives in ward care of these patients *were to prevent death to minimize heart muscle damage* and to return as many men as possible to duty with as little loss of time as compatible with their future health Routine care was divided into four stages Stage 1 As soon as diagnosis was established patients were confined to bed and given *sodium salicylate 1 6 Gm with sodium bicarbonate 0 6 Gm.* every four hours day and night Salicylate therapy was maintained until all clinical signs of rheumatic activity had disappeared and blood sedimentation had remained normal two weeks Drug therapy was then abruptly discontinued Stage 2 Patients were observed closely for one week to detect effect of salicylate withdrawal Patients were allowed to go *to the toilet in a wheelchair to avoid use of a bedpan* If there was an exacerbation of clinical symptoms or marked rise in blood sedimentation rate patients were demoted to stage 1 and sodium salicylate administered again for at least two weeks Stage 3 When patients had remained free from clinical and laboratory signs of active disease for one to two weeks after withdrawal of salicylate they were allowed unrestricted toilet privileges and permitted to sit in a chair on the ward or in the sun on an uncovered deck Recovery was usually *progressive however occurrence of exacerbation* in rare instances required demotion to stage 1 Stage 4 When patients appeared free from active disease for four weeks they were given light ward detail for two weeks If there was no marked rise in pulse rate they were allowed to return home for two weeks and advised to engage in normal activities but to avoid severe physical strain On return from leave *they were rechecked If free from symptoms with a normal* pulse rate and without valvular disease they were considered *fit for duty after one week s observation*

Sulfonamides are contraindicated in rheumatic fever are of no prophylactic value once a throat infection is established and may possibly modify the host in some way which favors the development of the rheumatic mechanism

were definite mitigation of suppuration in the skin lesions and a lessening of the ocular and pulmonary complications

Instead of a true pustular stage there was a vesicular stage in which the vesicular fluid was slightly milky and not yellow even in patients who died The process was later one of desiccation and desquamation rather than of pustulation and scabbing Five patients had a serious ocular discharge one being frankly purulent However in contrast to the panophthalmitis which so often develops these lesions completely healed there being no ulceration visible even at autopsy Chemotherapy also eliminated the classic secondary rise of temperature which usually occurs about the ninth or tenth day Residual cutaneous lesions of patients who recovered were merely slowly fading macular erythemas with extremely minute pocking but it must be admitted that in these the disease was modified

It is believed that the suppurative stage can be greatly reduced and often abolished and the incidence of other complications due to sulfanilamide sensitive organisms e g bronchopneumonia and conjunctivitis considerably lessened by sulfanilamide Lessened suppuration also will lead *to reduction in scarring*

STREPTOCOCCIC INFECTION

Food Borne Streptococcus Outbreak. V A Getting S M Wheeler and George E Foley (Boston) report a ham borne outbreak of streptococcic infection among persons attending a church function There were 24 cases of scarlet fever 56 of septic sore throat 7 of diarrhea 4 of vomiting 3 of nausea and 8 of miscellaneous complaints Gastro intestinal symptoms predominated One of the hams served was cooked by a woman who was in the early pre eruptive stage of scarlet fever Lancefield group A Griffith type 2 hemolytic streptococci were revealed in cultures from the ground ham from the throat of the food handler and from the throats of nine patients Since gastro-intes

(9) Am. J P b H lth 33 1217 12 3 Oct b 1943

several months In mildest forms however there often is no scarring Distribution of lesions tends to be centrifugal and they are especially numerous on the face fore arms and below the knees Confluence of lesions brings about edema another feature of smallpox Smallpox lesions also attack certain mucous membranes as is the case in chickenpox but they do so more extensively Instead of a few spots on the palate there may be numerous lesions there as well as on buccal mucous membrane and tongue and over the posterior pharyngeal wall Over any area where there is irritation of the skin surface lesions are likely to show well demarcated confluence

Blood count offers nothing reliable in differential diagnosis in early stages In purpuric smallpox white cell counts of 16 000–46 200 have been recorded in later stages The pustular stage of smallpox is accompanied by a marked leukocytosis

There is no single feature aside from specific laboratory tests that can be relied on under all conditions to differentiate chickenpox and smallpox The complete picture must be carefully studied and the patient and the lesions carefully examined Rate and manner of maturation of lesions must be considered It is important to realize how mild smallpox can be in certain instances

Smallpox Treated with Sulfanilamide J D Cottrell and H T Knights (N Z M C) describe the effects of sulfanilamide on 11 cases of variola of varying severity An initial dose of 2 Gm sulfanilamide was given followed by 1 Gm every four hours this dose being reduced to 1 Gm three times a day on improvement Treatment was instituted as soon as the vesicular stage was reached and the average total dose was 22 5 Gm during six days No serious toxic effects referable to sulfanilamide were seen

The main if not sole effect of sulfanilamide appeared to be reduction of complications due to pyogenic organisms no effect was detected on the essential virus There

(8) J Roy Army M C ps 81 7 15 J ly 1943

of granulomatous meningo encephalomyelitis frequently associated with myocarditis and chorioretinitis Two cases occurred in children of 6 and 8 years and the remaining three in adults in two of which the disease assumed an exanthematous form

The disease has generally been encountered in cities being found at autopsy and later in hospital cases but some patients or their parents had resided in suburban or rural sections This fact seems to be of great importance from the epidemiologic point of view As the parasite is found in a number of animals some of which come in contact with man it seems clear that these animals constitute a source for human infection It is not known how the disease is transmitted to man or from animal to animal Besides the direct digestive route there is possibility of transmission by insects among them the ticks ixodidae Favoring the concept of transmission by a vector is the finding of toxoplasmas in the red cells of birds and in histiocytes of the subepidermal region in experimentally infected animals

When clinical suspicion arises diagnosis must be confirmed by injecting the patient s spinal fluid or blood into experimental animals Guimaraes reports two cases

CASE 1—Youth 18 residing in the country had been ailing for 37 days There were high fever headache paresis of lower extremities sphygmothermal dissociation cervical rigidity dysphasia dyspnea and monocytosis Autopsy showed encephalitis pericarditis hypertrophy of left ventricle hepatitis splenitis nephritis and bronchopneumonia on the right side

Parasites in slides of the brain were free or enclosed singly or in small numbers in polynuclears and macrophages or assembled in pseudocysts They presented themselves generally as falciform bodies (crescents) fusiform and oval elements They were 4–4 5 microns long and 1–1 5 microns wide The protoplasm was stained blue by Giemsa s stain and the single nucleus purple. Binuclear forms represented parasites multiplying by longitudinal division

CASE 2—Girl 14 months residing in a suburb was born with hydrocephalus She had fever diarrhea agitation tremors of the right arm convulsions and tremors of the eye

tinal symptoms are not emphasized in the literature on food borne outbreaks of scarlet fever and frequently are not even mentioned possibly ham provides a medium which is more favorable for the production of an enterotoxic substance

TETANUS

Tetanus Immunization Dosage of Alum Precipitated Toxoid and Use of Fluid Toxoid after Trauma John J Miller Jr and J B Humber[1] (Stanford Univ) report that three injections of alum precipitated tetanus toxoid at three monthly intervals initiate and maintain for one year high antitoxin titers between 0 1 and 1 unit This level is probably protective even if reinjection is impossible or is omitted because of parental negligence at the time of trauma Two injections of alum precipitated toxoid do not result so regularly in maintenance of such high titers for a year A basic course of three injections and annual reinjection with alum precipitated toxoid are therefore recommended for children

When laceration occurs in any individual previously given injections of either alum precipitated or fluid tetanus toxoid a stimulating reinjection with fluid tetanus toxoid is preferred to one with alum precipitated toxoid because the desired rise in antitoxin is more rapid

TOXOPLASMOSIS

Human Toxoplasmosis Toxoplasmic Meningo Encephalomyelitis Occurrence in Adult and in New Born F Nery Guimarães (Rio de Janeiro) reviews 5 doubtful and 15 certain cases described in the literature Of the latter 10 were congenital and occurred in new borns or in infants only a few months old Mothers who could be examined were invariably healthy suggesting that the disease may present a latent form The disease consisted

(1) J Pediat. 23 516 521 November 1943
( ) Act med Rod J n 11 127 131 Aug Sept. 1943

death In all experiments administration of the drug varied from six to nine days there was no indication that the longer period was advantageous

Trials with other sulfonamides were not sufficiently extensive to permit final conclusions With sodium sulfadiazine nearly all mice of a small batch were cured when treatment was commenced the fifth day Sulfathiazole in oil started on the tenth twelfth thirteenth or fourteenth day after infection cured no mice but blood levels obtained were perhaps too low for maximal benefit

Although the drugs used produced cures in the animals treated there was no proved case of sterilization of the infection for in every instance tested the cured mice were found to be carriers Toxoplasmas were present in the brain usually being quite numerous and shown in every test to be virulent by passage to new mice This result was obtained whatever the drugs used and also seemed independent of length of administration and dose

Results of these experiments appear to warrant use of sulfonamides in treating human acute toxoplasmosis even though they cannot be relied on to eradicate the carrier state

TYPHUS

Experiences in Improvised Preparation of Convalescent Serums for Treatment of Typhus are reported by R Meyer In 94 patients with typhus treated with doses of 125 cc convalescent serum given intravenously on the second or third day the mortality rate was 6 4 per cent compared with 14 7 per cent in a control group Cases in which the agglutination titer was less than 1 800 were excluded

There were 464 donors from each of whom 200-400 cc blood was taken usually on the fourteenth to sixteenth day after the end of the fever Blood of compatible groups was mixed small amounts of residual agglutinins for red

(4) Ztsch f Imm tat f sch pe The ap 103 169 174 J ly 5 1943

balls Roentgen films showed small foci of cerebral calcification and deficient ossification of extremities of the long bones The spinal fluid was xanthochromic and rich in albumin and cells Because of suspicion of toxoplasmosis guinea pigs and white mice were inoculated with some of the spinal fluid and toxoplasmas were isolated from more than half of the animals She died elsewhere and autopsy was not done but there was little doubt that she had the disease

Therapeutic Cure of Acute Experimental Toxoplasmosis in Animals Toxoplasmosis is almost invariably fatal in man A principal cause for failure of therapy may be the short period in which patients were available for treatment since death has often followed appearance of initial symptoms within a few days Practically therefore decidedly beneficial results in man may be expected only from drugs which in animals have been proved effective when administered during the acute stage and shortly *before death*

David Weinman and Robert Berne (Harvard Univ) studied effects of appropriate sulfonamides in experimentally infected mice The period of expected survival was determined and the initial dose given to some animals at the expiration of the first third of this period to others at the end of the second third and to others at various later intervals Untreated controls died in an average of 15 days so the first series of infected animals did not receive treatment until the fifth day after infection Results with sulfapyridine were striking Of 17 mice given sulfapyridine in oil or sodium sulfapyridine 16 survived throughout the observation period of 28 days Of six untreated controls one recovered unexpectedly but the others died In a second series the five controls died in an average of 16 days Of six treated mice given sulfapyridine in oil 10 12 13 or 14 days after infection three died in the same period as the controls but three survived during an observation period prolonged to 85 days Of these mice two received *the first treatment as late as the thirteenth day* after infection i e three days before their anticipated

(3) J A M A 1 4 6 8 Jan. 1 1944

the efficacy of a chemical substance called V147 which is para sulfamidobenzamidine hydrochloride and of the corresponding amidoxime V186 and related substances

V147 was found to have a definite action on the infection of these mice with rickettsiae of murine and epidemic typhus It prevented development of the discrete pulmonary lesions which followed intranasal inoculation or greatly reduced their size and number and prevented death in mice which had received heavier inoculations of virus intranasally or (murine strain) intraperitoneally The drug was effective when given intraperitoneally subcutaneously or with food Its effect though more striking when given before infection was demonstrable if administration was delayed until 42 hours after infection V186 was as effective in controlling typhus infection in mice as was V147 possibly a little more so Ten other closely related compounds also showed activity but none had greater activity than V147 and V186 and most had less The chemotherapeutic property appears to be highly specific because any considerable modification of the molecule at once abolishes activity The drugs were ineffective in typhus infected guinea pigs

A trial with V147 and V186 during an outbreak of human typhus in Naples proved disappointing No therapeutic benefit could be shown Possibly one factor contributing to failure was the great difficulty in beginning treatment within the first few days of the disease Another was the unexplained toxicity of the drugs in occasional typhus patients

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VIRUS DISEASES

Rickettsial Diseases are discussed by R E Dyer (Bethesda Md) Rickettsiae are gram negative microorganisms coccoid or bacillary found typical in arthropods Those known to be pathogenic for man occur intracellularly in tissues of their animal and arthropod hosts

(7) J A M A 124 1165 117 Ap 2 1944

blood corpuscles could be ignored since the blood of the *recipient could neutralize many times the amount con* tained in 125 cc serum The blood mixture was kept at room temperature, this was 35 6–42 8 F during early stages of the tests The serum was drawn off and passed through a Seitz E K filter which could be sterilized by a current of steam The front plate which was likely to escape sterilization was heated by a blow lamp before hand Serum separated by standing in the cold contained a little hemoglobin and tended to become turbid and flocculent after a few weeks

When room temperature rose to 53 6 F addition of phenol to the serum was contemplated but experiments on healthy persons showed that normal serum with addi tion of 0 4–0 5 per cent phenol caused unpleasant reactions when given in requisite doses smaller quantities of phenol proved inadequate A high efficiency centrifuge was there fore necessary when low temperatures were not available to obtain serum quickly and so avoid undue multiplication of bacteria Each flask of serum containing *250* cc was tested for sterility by aerobic and anaerobic cultures ob served over eight days

Use of Atabrine in Typhus Fever Harold Freed (Dal las Tex) reports two additional cases of typhus fever in which atabrine had a prompt and distinctly favorable effect Fever was markedly reduced in both within 48 hours after beginning therapy Freed previously reported two cases in which atabrine had a similarly beneficial *effect While this series of four cases is small there is* nevertheless strong suggestion that atabrine has a certain therapeutic value in typhus fever

Substances Chemotherapeutically Active against Ty phus Rickettsiae C H Andrews H King M van den Ende and J Walker[6] (*Nat l Inst for Med Research*) in fected anesthetized mice intranasally with dilute rickettsial suspensions causing discrete lung lesions They then tested

(5) M B U V t Adm 0 119 121 Oct be 1943
(6) La cet 1 777 781 J e 17 1944

strains No strain of Bacillus proteus has been found which is agglutinated by Q fever serums and production of agglutinins in trench fever is as yet unknown There are definite immunologic differences illustrated by absence of cross immunity which separate the subdivisions of the rickettsial infections

Clinically typhus spotted fever and tsutsugamushi groups are characterized by sudden onset rash fever of fairly well defined duration mental disturbance and pronounced prostration

The typhus subdivision of rickettsial infections comprises the epidemic or louse borne type and the endemic murine or flea borne type The Rocky Mountain spotted fever subdivision is not so clearly delineated but includes in addition to Rocky Mountain spotted fever other identical or similar tick borne diseases such as boutonneuse fever the misnamed São Paulo exanthematic typhus Tobia fever of Colombia Kenya typhus and possibly the so-called tick typhus of India and South African tick bite fever The tsutsugamushi subdivision embraces in addition to the type disease that known as scrub typhus and other mite borne diseases of southern Asia and the islands of the Southwest Pacific

Typhus is the rickettsial disease of greatest military importance The Rocky Mountain spotted fever group is apparently not of much military significance though cases have occurred in military personnel and the tsutsugamushi group is occurring to some extent among troops in the southwest Pacific zone

Insects and Their Allies as Causative Agents and Transmitters of Disease Ernest Carroll Faust (Tulane Univ) divides these into three classes (1) species which venenate or introduce toxins into the body (2) species which actually invade the body producing infestations (3) species which carry pathogenic micro-organisms and introduce them into the body

The group of arthropods most important medically are

(8) N rthwest Med. 42 250 257 September 1943

These organisms have never been cultivated on artificial mediums free from living cells but they grow and multiply in various tissue culture mediums Except the rickettsia of Q fever they do not pass filters that retain pathogenic bacteria Several species not known to be associated with any disease of man or other animal have been described One species is pathogenic for lower animals but not apparently for man—Rickettsia ruminantium the causative agent of heart water disease of sheep goats and cattle Identification of these organisms is based on appearance staining reactions and occurrence in arthropods Bodies resembling rickettsiae have been isolated in cases of trachoma and psittacosis and while there is no conclusive evidence on which to base classification it is possible that further knowledge may place them in the class rickettsia

Diseases of man with which species of rickettsia are associated and of which the epidemiologic character is determined by life cycles and feeding habits of the arthropod vectors may be divided into typhus Rocky Mountain spotted fever tsutsugamushi and Q fever Q fever stands a little apart differing somewhat from other rickettsial diseases clinically and in that the organisms readily pass through bacterial filters which retain other strains of pathogenic rickettsiae Trench fever has often been classified as a rickettsial disease since it is louse borne and rickettsiae have been described in lice and their feces which subsequently have infected volunteers Opportunities for careful study of trench fever until recently have been lacking since it disappeared with the close of World War I

A characteristic of this group of diseases excepting Q fever is production in patients of agglutinins for the X strains of Bacillus proteus (Proteus vulgaris) This agglutination of B proteus X (Weil Felix reaction) has assisted in distinguishing the tsutsugamushi group from the typhus and spotted fever groups since with tsutsugamushi agglutinins for the OXK strain of Bacillus proteus are typically produced while serums of patients with typhus and spotted fever agglutinate the OX_{19} and OX_2

and Rhodesian both transmitted by the tsetse fly in one of two ways Within a few hours it may discharge still living trypanosomes from the soiled proboscis into a second human being After that there is an incubation period of approximately *12* days in the midgut of the tsetse *fly* before these organisms now greatly multiplied are available for reinoculation of human beings Then they are disgorged in the insect s saliva American trypanosomiasis is transmitted by the assassin or kissing bug This bug does not directly inoculate the trypanosomes when it takes a blood meal rather as it takes up blood it defecates on the skin causing considerable itching Scratching causes pathogens to be rubbed in Commonly the bug takes its blood meal at the outer canthus of the eye and the organisms enter that site

Rickettsial infections the typhus group of fevers are transmitted by arthropods Epidemic typhus is louse transmitted Spotted fever is tick borne The organism lives continuously in the tick and man usually gets the infection from the bite of an adult tick Japanese river fever another rickettsial disease is transmitted by a red mite *trombidium Q fever is tick transmitted sometimes by* the same tick which transmits tick borne spotted fever Trench fever is possibly a rickettsiosis and is louse borne Murine typhus is transmitted by the tropical rat flea

Other soft bodied ticks (ornithodorus) are transmitters of endemic relapsing fever produced by a spirochete epidemic relapsing fever is transmitted by the body louse The tropical rat flea the transmitter of murine typhus is also the most common transmitter of bubonic plague The etiologic agent Pasteurella pestis is taken up by this flea from wild or semiwild rodents Sooner or later the infection through the rat flea gets into domestic rats and from domestic rats through this flea to human beings

Viruses, Fungi, Protozoa and Insects are in the opinion of A E Taft (Bryn Mawr) closely related He has

(9) P syl a M J 47 26 32 O t b 1943

insects or their allies which are vectors or incubators of pathogenic micro-organisms producing serious diseases in man This group has two subdivisions those that are merely mechanical transmitters and those which are alternating hosts with man and reservoir hosts in the life cycle of the micro-organism

The common house fly Musca domestica is representative of all filth flies which on legs and mouth parts wings and in the body carry countless disease producing organisms There is definite evidence that such enteric infections as typhoid and paratyphoids bacillary and amebic dysentery and cholera are in many places particularly in the tropics and Orient commonly transmitted mechanically by flies tetanus and anthrax are similarly transmitted The spores of these pathogens are carried internally by flies picked up by maggots and remain until the fly matures Then the pathogen may be deposited in an open wound Certain so-called eye gnats also transmit disease mechanically They feed primarily on exudate from the conjunctivas and are responsible for epidemics of acute conjunctivitis and possibly trachoma

Several of the most important diseases in which the arthropod is host in the life cycle of the disease organism are transmitted by mosquitoes e g malaria yellow fever dengue and filariasis Among others are hemoflagellate infections including *kala azar* or *visceral leishmaniasis* Delhi Aleppo or oriental sore with cutaneous manifestations and espundia producing a cutaneous lesion that later frequently metastasizes to produce a mutilating mucocutaneous lesion All these leishmaniases are transmitted by the sandfly phlebotomus which multiplies in the midgut of the fly and then may return to the anterior part of the digestive tract whence it is introduced in minute droplets of saliva into the skin of man Other hemoflagellate infections include three types of trypanosomiasis two of which are African trypanosomiasis or African sleeping sickness and the third American trypanosomiasis or Chagas disease The African types are the Gambian

tive or neutralizing antibodies of the blood Their import to immunity is not the same under all circumstances and their presence is no guarantee of complete immunity Although the relationships of antibody and immunity to virus infection may seem confused when all infections are grouped together when considered in terms of the mechanisms of different infections an orderly concept evolves

There is clearly need for considering protective action of antibodies in terms of the pathogenesis of the particular infection whether the agent attacks cells which are comparatively extravascular or cells intimately associated with circulating blood cells readily reached by outside agencies or essentially by way of the vascular system If the virus effects its entry into an environment where antibodies are readily available it is prevented from establishing itself either locally or at a distant point and immunity to infection obtains protection of specific cells results in general immunity If antibodies are not effective at the portal of entry but are present in the circulating blood infection can occur with or without characteristic signs of the disease When the injury at the portal of entry constitutes the essential manifestation of virus action both infection and clinical disease occur though the latter may be limited when establishment of virus at the primary site constitutes merely the starting point for its dissemination to distant tissues where the conspicuous damage takes place infection occurs but the typical disease is prevented

Differences in the mechanisms of infection and in availability of antibodies offer an explanation for the ability of antibodies to maintain prolonged immunity in certain instances and an impermanent effect in others Availability obviously involves quantitative factors in that with high concentrations of circulating antibodies they may also become available in sufficient quantities in secretions which cover an exposed tissue or in other body fluids—as antibodies to influenza virus increase in nasal secretions following infection or vaccination—to protect the susceptible

sought to prove this by correlating various observations

	Fungi Protozoa	Viruses
Distribution	Universal	Universal
Habitat	Damp regions dead vegetable matter	Rural forest and swamp
Nucleoprotein	Multiplies on spore germination	Largely composed of nucleoprotein
Enzymes	*Synthesized in great variety on spore germination*	Viruses act like enzymes
Mutation	Constantly takes place in fungi	Occurs with frequency in viruses
Carbohydrate	Necessary food for fungi	Viruses follow its translocation in plants
Insects	Both fungi and protozoa are in intestinal tract of insects and also externally	Prominent factor in virus disease
Rodents	Fungi as food Protozoa as parasites	Viruses commonly associated with rodents
Common cold	Spores in air cause perennial rhinitis cured by spore vaccine	A virus-caused condition
Papillomas	Human perigenito anal papillomas caused by intestinal protozoa	In rabbits skin papillomas are a virus disease
Swine influenza	In earthworms which harbor nematodes	Derived from lung worm ova (nematode) and earthworms
Toxoplasma	A protozoan	A neurolytic" filtrable agent derived from toxoplasma
Inclusion bodies	Morphologically identical with encapsulated phase of protozoan life cycle	Virus derived from inclusion bodies of fowlpox

Immunity to Virus Diseases Thomas Francis Jr[1] (*Univ of Michigan*) *comments that in attempting to* understand why immunity is long lived or transient following different virus infections considerable attention has been given to the immunologic significance of protec

(1) Yale J Biol. & Med. 16 401-413 May 1944

any connection between them Neither Russian nor louping ill virus appeared to be related to the other viruses tested

Viruses of Japanese B St Louis and West Nile types of encephalitis as a group showed a certain relationship but not so close as that between the Russian and louping ill viruses In complement fixation tests besides homol ogous reactions Japanese serum brought about reactions with both St Louis and West Nile antigens St Louis serum reacted with Japanese antigen and West Nile serum with Japanese antigen In neutralization tests with mouse serums no relationship was found among these three viruses while in similar tests with either hamster or guinea pig serum—which gave higher homologous titers—it was found that Japanese serum protected against West Nile and St Louis viruses St Louis serum against West Nile virus and West Nile serum against Japanese virus In intracerebral and intraperitoneal cross resistance tests no relation was found between these three viruses More over Japanese B St Louis and West Nile viruses appeared unrelated to any one of the three other viruses tested

Western equine encephalomyelitis virus stood apart in all tests as unrelated to any of the other viruses studied

Homologous titers of complement fixing antibodies in mouse serums showed a gradual decline with passing of time after vaccination and this loss of homologous titer was paralleled by a similar drop in titer of heterologous reactions In the case of Japanese B St Louis and West Nile viruses with which at the start the amount of cross ing was not high a point was reached beyond which heterologous reactions could no longer be detected

Comparison of specific levels of complement fixing and neutralizing antibodies for viruses in mouse hyperimmune serums showed difference in rate of persistence Comple ment fixing antibodies which had highest titers on the tenth day diminished gradually until on the fiftieth day all titers had reached levels from one fourth to one eighth of their values on the tenth day Conversely levels of neu

cells at the portal of entry and thus provide immunity to the body as a whole The amount of virus available for infection and multiplication at the original site may thus be considered inversely proportionate to the amount of antibody readily available at that location

Another factor not ordinarily measurable in clinical and pathologic terms though seriously influencing duration of immunity to the same disease is homogeneity of the virus involved Prolonged immunity against a generalized virus infection such as measles is related not only to persistence of antibodies but to the fact that the strains of virus exhibit little qualitative variation they are immunologically homogeneous Conversely when a disease is encountered in which repeated attacks occur although the virus is introduced into the blood stream and disseminated thereby but disappears with subsidence of the disease the probability is strong that failure of antibodies to maintain resistance will be associated with existence of multiple immunologic types

The concept that duration of immunity is determined by continued presence or absence of virus in the recovered animal seems more difficult to support in the light of present knowledge than is an interpretation in which the deciding influence is assigned to the availability of antibodies

[This discussion by Francis is a pleasing and timely one. It is simple clearcut and logical at a time when much confusion of ideas is prevalent.—Ed]

Immunologic Relationship among Central Nervous System Viruses were studied by J Casals[2] (Rockefeller Inst) Observations were made on viruses of Russian spring summer encephalitis louping ill Western equine encephalomyelitis and Japanese B St Louis and West Nile types of encephalitis

Russian encephalitis and louping ill viruses showed a close relationship by complement fixation neutralization and intraperitoneal cross resistance tests Intracerebral cross resistance tests on the other hand failed to reveal

(2) J Exp Med. 79 341 359 April 1944

and during incubation be termed treatment whether or not one can demonstrate presence of the disease agent in the exposed susceptible subject at the time of treatment.

Bullis Fever (Lone Star Fever — Tick Fever) An Endemic Disease Observed at Brooke General Hospital, Fort Sam Houston, Tex. John C Woodland Mordecai M McDowell and John T Richards in the spring and summer of 1942 observed a group of patients acutely ill with a clinical disease which defied definite identification No report of similar cases could be found Several out standing clinical features were characteristic an unusually low white blood cell count with moderate neutropenia severe postorbital and occipital headache and constant lymphadenitis varying from involvement of a few glands to general lymphadenopathy All the soldiers gave a history of having been on maneuvers at Camp Bullis Tex a week or more prior to onset of symptoms In all cases there was evidence of multiple tick bites especially on the legs and thighs In many instances ticks were still clinging to the skin The tick was identified as Amblyomma americanum the Lone Star tick

There were no deaths the disease being self limited The syndrome varied from a mild febrile illness of short duration to a severe debilitating prolonged disease with a protracted convalescence In more severe forms a rash resembling German measles and at times typhus appeared early but disappeared within 48 hours In about 10 per cent of cases skin manifestations developed Elevation of temperature usually continued about five days and re turned to normal by lysis Temperature remained normal except in a few instances in which an occasional rise to 99 F was noted The incubation period was 7–10 days Treatment was symptomatic and no complications or sequelae were noted

These cases of Bullis fever resemble somewhat those of Colorado tick fever In the latter however a typical saddle back type of fever curve was noted Lymphadenop-

(4) J A M A 122 1156-1160 A g 21 1943

tralizing antibodies for the same samples of serum were on the fiftieth day as high as or higher than those found on either the twenty fifth or the tenth day save in the case of Japanese B virus

The state of immunity of animals following vaccination with the viruses studied was found to be different at a given time depending on the method used to determine it Thus mice vaccinated with St Louis virus had positive complement fixing antibodies on the tenth day and no neutralizing antibodies The state of immunity changed with time. Hence it is believed that to detect whether two viruses are related or not multiple observations are necessary over a considerable time employing all available methods of immune comparison

Use of Immune Bodies in Treatment of Certain Infectious Diseases (Virus and Rickettsial Diseases) Caused by Intracellular Parasites, with Emphasis on Need for Early Diagnostic Criteria of Infection. Joseph Stokes Jr reports effective use of gamma globulin from large pools of normal adult plasma for attenuation of measles even when injected after onset of fever and appearance of Koplik s spots but before appearance of rash This indicates the need for development of earlier diagnostic criteria for this disease and possibly for other diseases caused by intracellular parasites Data bearing on epidemic influenza type A in mice and ferrets and on poliomyelitis *in mice (Lansing strain) also emphasize* the need for additional studies in these diseases It is anticipated that with development of more concentrated and effective homologous antibody preparations and earlier criteria of disease additional intercellular parasites will be brought under more effective therapeutic control

In view of the confusion in terminology used by clinicians and the need for earlier diagnostic criteria and treatment it is suggested that the term prophylaxis be limited to use of immune bodies previous to exposure of the susceptible individual and that their use following exposure

(3) Yale J B ol. & Med. 16 415 4 4 M y 1944

Virgin Islands was milder and conferred practically no immunity The type occasionally encountered in the United States seems about midway between these

The form of the disease seen in the South Pacific runs a self limited course for 6-11 days average 9 days Typically onset is acute usually with mild chill lasting 5-10 minutes followed by rise in temperature to 103 or 104 F There is remission of temperature after two or three days frequently associated with development of a morbilliform rash Within 24 hours temperature rises again usually to its original level Fever remains 48-72 hours and then temperature drops by crisis and remains normal except for an occasional slight rise on the eighth day

In a large series of cases the commonest symptom was backache (92 per cent) Prostration of varying degrees was present in most patients Pain behind the eyes (88 per cent) was distinct from frontal headache (86 per cent) Anorexia occurred in 87 per cent and was almost absolute in some patients Aching joints (70 per cent) were undoubtedly due to periarticular involvement probably in tendons A slight but definite chill marked the onset in 62 per cent Nausea was experienced by 45 per cent but vomiting was infrequent (13 per cent) Sore throat (28 per cent) and pruritus (21 per cent) were relatively common Pain in the left side of the abdomen was recorded in 17 per cent this was usually described as a dull ache most intense opposite the umbilicus but affecting most of the left side usually lasting about 24 hours

Physical examination revealed little except lymphadenopathy rash and frequently bradycardia Splenomegaly was not noted The typical temperature curve described in textbooks occurred in only 51 per cent The most characteristic laboratory finding was decreased leukocyte count being below 6 000 in 71 per cent Reduction in almost all cases was at the expense of granular cells Sedimentation rate was within normal limits in 94 per cent Urine was normal in all cases Red cell count and hemoglobin were not affected

athy a constant finding in the Texas cases was not reported in Colorado tick fever Dengue fever was thought of as a possibility but absence of exposure to mosquitoes and the clinical course aided in ruling out this condition Malaria was considered in view of the leukopenia chills and fever but this too was ruled out by the clinical course and negative blood smears Acute mononucleosis was excluded by the negative heterophil antibody reaction absence of sore throat and failure to find the typical white blood cells Typhus and Rocky Mountain spotted fever were discarded as possibilities in view of the clinical course and absence of laboratory findings in blood specimens

Hence the authors believe that Bullis fever constitutes a new entity not heretofore described All the men gave a history of repeated and prolonged exposure to tick bites while in the area of Camp Bullis which has a heavy tick infestation Although no positive proof of association of bites of Amblyomma americanum with this disease has been established it is believed further laboratory investigation will prove that it is transmitted to man through the tick bite

Since there will be heavy troop concentrations in rural areas during the war and since it is believed this disease is more widely distributed than has been recognized attention of medical officers should be called to its occurrence During May and June 1943 485 patients with the syndrome were admitted to the hospital at Fort Sam Houston A higher percentage of patients in this later group manifested the more serious symptoms and there was one fatality In the patient who died the terminal clinical picture was that of severe agranulocytic angina and septicemia

Dengue Observations in South Pacific Area. John R Cavanagh (M C U S N R) states that dengue varies in different parts of the world The form observed in the Philippines was apparently much more severe than that seen in the South Pacific area That seen in Puerto Rico and the

(5) W r Med 4 549 555 De mber 1943

first few days The dengue carrying mosquito bites by day as well as by night hence protection is needed throughout the 24 hour period Men active and moving about are not so likely to be bitten

There is no specific treatment For symptomatic relief of aches and pains ½–1 gr codeine sulfate with 10 gr acetylsalicylic acid seemed most effective Morphine sulfate is occasionally necessary in more severe forms Large amounts of fluid are helpful but are difficult to administer because of reluctance of the patient to take them Sulfonamides have no effect except occasionally to increase nausea or anorexia

Spironema of Cyprian Relapsing Fever The vector of infection in a series of cases of relapsing fever among troops in Cyprus was shown in all probability to be the tick Ornithodorus tholosani and the infection was generally acquired by men sleeping in earth shelters or caves Urobilinuria was an almost constant symptom and the Kahn reaction was positive in about 20 per cent of cases

K C Dixon successfully transmitted the spironema to guinea pigs proving that the relapsing fever was tick borne since only this variety of the disease can infect the guinea pig The strain of spironema isolated caused heavy infection in 4–12 days after intraperitoneal inoculation The heavy infection in which the blood is teeming with spironemas persists for about three weeks the blood remains infective longer however as successful passage can be achieved later The rat also may be infected but apparently does not show heavy infection

The spironema is best studied by suspending blood from a heavily infected guinea pig in human citrated serum and then examining by dark field illumination Under these conditions the spironema remains alive and actively motile for at least 48 hours It can be readily observed in the clear serum apart from the clumps of agglutinated corpuscles

Alive the Cyrian spironema has a wavelength of about

(7) J Roy Army M Corps 81 89 92 August 1943

The disease is transmitted by the Aedes egypti mosquito which is widely distributed throughout the South Pacific The usual incubation period given for dengue is 7–10 days The shortest period in which the disease could have de veloped was seven days In 5 per cent of the patients it developed within seven days of arrival Twenty three per cent had been on the island 14 days or less Five per cent had been there 11–12 months before contracting the dis ease There was no instance of reinfection

Complications are unusual but the following were ob served hemorrhagic nephritis trismus of the jaw ar thritis of the hip suppuration of glands bradycardia pur puric manifestations and evere meningismus after the patient had been afebrile for one week Postdengue neuras thenia was almost invariably present persistence depended on severity of the disease ranging from three to six weeks It was characterized by anorexia muscular weakness in somnia lack of ambition and depression

Diagnosis is relatively easy in epidemic dengue The only diseases likely to be confused with it are malaria and measles In sporadic cases diagnosis is more difficult In *presence of severe backache and pain behind the eyes fever* and leukopenia diagnosis of dengue is justified Pain be hind the eyes is characteristic and seldom encountered in other conditions If the temperature then runs the typical febrile course with normal sedimentation rate diagnosis is confirmed

Primarily prevention depends on elimination of the aedes mosquito Its occurrence is so widespread in heavily infected areas that local measures should be strictly en forced including sleeping under a net being fully clothed at all times spraying wards living quarters and foxholes with insecticide repairing mosquito netting immediately and reporting immediately if not feeling well The last was considered most important because many men waited for several days before reporting at sick bay and thus con stituted a potent source of infection Dengue is supposed to be most infectious during the prodromal stage and the

have seen seven cases of rat bite fever in New York City in the last few years There are two types one caused by Spirochaeta morsus muris called sodoku and the other

DIFFERENTIAL DIAGNOSIS

	S u	H ve hil F ve
Causative organism	S morsus muris	S moniliformis
Transmission	Bite of rat occasionally other animals	Bite of rat or other animal possibly contaminated food
Incubation period	5–30 da. Av 13 da	2–10 da Av 5 da
Wound from bite	Apparent healing followed by chancre like ulceration	Heals promptly without induration or exacerbation
Lymph glands	Regional lymphadenitis	Not involved
Systemic manifestations	a) Regularly relapsing fever	a) Intermittent but not regularly relapsing fever
	b) Generalized maculopapular rash	b) Macular and petechial eruption
	c) Varying degrees of prostration and debility	c) Varying degrees of prostration
	d) Arthritis rare	d) Metastatic arthritis common
Laboratory findings	a) Polymorphonuclear leukocytosis	a) Same
	b) Secondary anemia	b) Same
	c) Kahn tests usually positive	c) Negative
	d) Isolation of spirochete by animal inoculation of blood or infected lymph	d) Isolation of S moniliformis by blood culture on veal infusion broth enriched with rabbit serum
	e) Negative agglutination	e) Positive agglutination with streptobacillus serum from patients agglutinates a polyvalent antigen
Treatment	Responds to arsenicals	Arsenicals of little value sulfonamides (?)

caused by Streptobacillus moniliformis called Haverhill fever (from the epidemic in Haverhill Mass in 1926) Any attempt to draw sharp lines of differentiation between the two types by clinical observations alone remains open

2 microns The regularity of the wavelength observed in the living organism does not obtain in fixed films The amplitude of the organism is only slightly shorter than its wavelength It has between 3 and 11 coils The living spironema of relapsing fever is very different in structure from that of Vincent s angina The latter when examined alive by the same technic has open irregular waves with a wavelength of about 6 microns The Cyprian spironema occurs frequently in a wheel like annular form which makes a complete highly motile circle A fine thread joins the two ends of the spironema so that probably the circle is produced by entanglement of the terminal flagellae of one organism

Effects of Roentgen Rays on Cell-Virus Associations William F Friedewald and Rubert S Anderson[8] (Memo rial Hosp New York City) report that the virus induced papillomas of cottontail as well as domestic rabbits regress completely within a few weeks when exposed to 5 000 r of x ray irradiation The x rays do not immediately kill the papilloma cells but lead to death by inhibiting cellular division and producing pathologic changes in the cells which then continue to differentiate However not only does the virus associated with the growths persist in un diminished amount during regression but often an in creased yield of it can be obtained on extraction

Fibroma virus in crude extracts or in vivo is inactivated by far less irradiation than papilloma virus Ten thousand r *destroys 90 per cent or more of the infectivity of the* fibroma virus whereas at least 100 000 r is required to inactivate 50 per cent of the papilloma virus in extracts containing about the same amount of protein

No variant of the papilloma virus or fibroma virus has been encountered as a result of irradiation

Rat Bite Fever Comparison of Spirochetal (Sodoku) and Bacillary (Haverhill Fever) Forms C Michael Witz berger and Herbert G Cohen (New York Med College)

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(8) J E pe Med 78 285 304, Octobe 1943
(6) A ch Pediat. 61 123 133 Ma h 1944

decreases and the amount present falls off slowly during two to four hours After this time no detectable amount remains in the circulating blood When penicillin is administered intramuscularly blood concentration reaches a maximum in 10–30 minutes This level is maintained one to two hours after which there is a gradual decrease and after two to four hours penicillin can no longer be detected in the circulating blood Although blood concentration is never as high after intramuscular injection a higher level is maintained for a longer period

Rapidity of excretion is a serious obstacle in therapy Suspensions in oil and subcutaneous implantation of solid pellets have been used successfully in animals but have not proved satisfactory in man Efforts have been directed toward preparation of compounds which will slowly release active penicillin into the circulation

Penicillin has been proved effective in man when given intramuscularly intravenously and intrathecally and when administered directly into joints and serous cavities as well as in local applications It is valuable in treatment of infections due to hemolytic streptococci pneumococci gonococci meningococci and staphylococci In particular it has proved effective in cases resistant to sulfonamides The number of patients so far treated is small but results are highly encouraging

Clinical Use of Penicillin Observations in 100 Cases are reported by Martin Henry Dawson and Gladys L Hobby[1] (Columbia Univ) Its efficacy in staphylococcic infections is important not because of a special sensitivity of staphylococci but because of the refractoriness of this type of infection to sulfonamide therapy A favorable often dramatic response was obtained in 15 of 18 cases of staphylococcic bacteremia the three fatal cases represented problems of great complexity Results in 19 cases of staphylococcic infection without bacteremia were equally impressive In three of four cases which failed to respond the infecting organism was subsequently

(1) J A M A 124 611 62 M 4 1944

to question However for simplification the authors present a comparison (see Table) which may aid in differential diagnosis

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PENICILLIN

Penicillin as Chemotherapeutic Agent Martin H Dawson Gladys L Hobby Karl Meyer and Eleanor Chaffee (New York City) report experiments on antibacterial activity of penicillin in vitro and in vivo toxicity absorption and excretion Penicillin is highly effective against gram positive organisms both aerobic and anaerobic and against gonococci and meningococci Not all strains of the same organism are equally sensitive but generally strains of pneumococci are more sensitive than those of hemolytic streptococci and the latter are more sensitive than staphylococci Action of penicillin appeared to be either bactericidal or bacteriostatic depending on conditions of the experiment It is active in extraordinarily high dilutions It is many thousand times as effective as any of the sulfonamides its activity being comparable to that of gramicidin and tyrocidin Penicillin is active in the presence of pus and inflammatory exudates

Toxicity was tested in mice guinea pigs rabbits dogs and man Additional experiments were carried out on tissue cultures and developing chick embryo No toxicity was observed with amounts far beyond the range of therapeutic dose. No toxic effects were observed in tissue cultures on the chorio allantoic membrane or applied directly to the human eye No untoward effects have been observed in man with doses up to 240 mg or 60 000 Oxford units *of a highly purified product*

Penicillin is rapidly excreted through the kidneys and frequent administration is necessary to maintain adequate blood concentration When penicillin is given intravenously there is rapid loss from the blood stream during the first half hour after injection Rate of disappearance then

(9) A n Int Med. 19 707 717 No ember 1943

pleural and intra articular routes were used with excellent results in empyema and suppurative arthritis In menin gitis penicillin should be administered intrathecally

Mild toxic reactions were encountered only occasionally Urticaria was observed in three cases and phlebothrombo sis in one These reactions were probably due to im purities in certain preparations and not to penicillin itself

Penicillin in Treatment of Experimental Leptospirosis Icterohaemorrhagica (Weil s Disease) Leptospirosis icterohaemorrhagica has been reported in nearly every civilized country Mortality rate varies from 5 per cent in Europe to as high as 55 per cent in Japan Probably many unrecognized cases have occurred in the United States While serum has been of some value in treatment it has not been uniformly satisfactory

In view of previous reports on effectiveness of penicillin against some spirochetal infections F R Heilman and W E Herrell examined its effect on infections due to Leptospira icterohaemorrhagiae in guinea pigs After pre liminary experiments to determine dosage and virulence of the infection 64 guinea pigs were infected with Lepto spira icterohaemorrhagiae Of 32 treated with penicillin none died of the disease but 3 (9 per cent) died of what appeared to be toxic effects of penicillin Of 32 untreated guinea pigs 29 (91 per cent) died of Weil s disease

Since as little as 0 5 cc infected blood could cause fatal infection and since the test animals were inoculated with four to six times this amount it is evident that penicillin protected against several times the lethal dose of the organism Although a number of febrile relapses occurred they promptly responded to further penicillin therapy Effectiveness of penicillin on thoroughly established in fections was shown in two guinea pigs inoculated with 3 5 cc infected blood and not treated until the third day after inoculation when both animals showed high tempera tures Treatment with 5 000 units of penicillin in divided doses per day for seven days resulted in prompt drop

(2) Proc Staff Meet M yo Cl 19 89 99 F b 23 1944

found to be resistant to penicillin in vitro In chronic osteomyelitis the results were satisfactory only when penicillin was used with adequate surgery One case of frank empyema and two cases with heavily infected pleural exudate were successfully treated without thoracotomy

Penicillin proved highly effective in treatment of pneumococcic hemolytic streptococcic gonococcic and meningococcic infections There were 28 patients who failed to respond to sulfonamide therapy or in whom sulfonamides were contraindicated In 9 of 10 cases of lobar pneumonia 2 of which showed signs of incipient empyema results were uniformly good The only failure occurred in a parturient woman with an overwhelming infection In this case the blood stream was sterilized within 12 hours and death apparently resulted from general toxemia One case of pneumococcic meningitis which persisted despite intensive sulfonamide therapy yielded promptly to intrathecal administration of penicillin The blood stream was temporarily sterilized in two cases of acute pneumococcic endocarditis treated early in the study with inadequate amounts of material In sulfonamide resistant gonococcic infections including gonococcic arthritis results were particularly striking Response in one case of meningococcic meningitis in which penicillin was not administered intrathecally was unsatisfactory Results in early cases of subacute bacterial endocarditis due to nonhemolytic streptococci were encouraging

In infections of mixed etiology results were less uniformly satisfactory A favorable response was obtained only in cases in which gram positive organisms played a dominant role Penicillin is not effective against gram negative bacilli It had no value in three cases of primary atypical pneumonia.

Data now available indicate that the most practical method of administering penicillin is by intramuscular injection at intervals of four hours In presence of severe sepsis intravenous administration may be necessary Intra

what ill 22 hours after inoculation when treatment was started Improvement was visible 24-36 hours after administration of penicillin was begun in treated mice while untreated controls were sicker The blood of treated mice showed marked reduction and in some instances total absence of spirochetes on the second day while the blood of untreated mice showed severe infection Of 28 untreated mice 21 died Of 26 treated mice only 1 died The treated animal that died had not had any spirochetes in the blood for several days and did not have the enlarged spleen commonly found in animals dying of the spirochetal infection cause of death in this instance is not known Untreated mice usually died the fourth day and the single treated mouse that died did so the eighth day after inoculation Of 7 untreated mice that lived all showed relapse as evidenced by blood smears while of 25 treated mice only 4 had a relapse It seems likely that if treatment had been continued longer than four days these relapses might not have occurred

It is evident that this strain of spirochetes of relapsing fever is sensitive to action of penicillin and it seems probable that penicillin will also affect other strains of this organism The authors hope that as a result of these studies penicillin may prove to be a more effective agent for treatment of relapsing fever than those previously used

Rapid and Sterilizing Effect of Penicillin Sodium in Experimental Relapsing Fever Infections and Its Ineffectiveness in Treatment of Trypanosomiasis (Trypanosoma Lewisi) and Toxoplasmosis Experiments on six rats inoculated with blood containing adult trypanosomes performed by Donald L Augustine David Weinman and Joan McAllister (Harvard Univ) revealed no difference in the parasite counts of four treated with large doses of penicillin and the two controls Trypanosomes in the blood of the treated animals appeared active and unharmed and infected other rats producing typical

(4) S 99 19 20 J 7 1944

in temperature which remained normal until they were killed 25 days after inoculation Examination showed no lesions of leptospirosis In these animals the relatively large doses of penicillin produced no evident generalized toxic effect

Results of these experiments suggest that penicillin may be useful in treatment of Weil s disease and other leptospiral infections in man

Penicillin in Treatment of Experimental Relapsing Fever Relapsing fever is a spirochetal infection that has occurred from time to time throughout the world It frequently is endemic but may become epidemic Louse borne epidemics are likely to occur under conditions of overcrowding filth and poverty Millions of people have been its victims especially under conditions imposed by war and immigration While arsenical therapy is satis factory its use is not without certain hazards Therefore F R Heilman and W E Herrell[3] studied the effects of penicillin

A single strain of relapsing fever spirochetes Bor relia novyi was used Mice were infected by intra *abdominal injection of 0 3 cc citrated or heparinized* rat blood containing great numbers of spirochetes obtained from rats the third day after inoculation This pro- duced a massive infection in mice with great numbers of spirochetes in the blood 24 hours after inoculation Pos sible presence of secondary invading bacteria in inoculated blood was ruled out by cultures on blood agar and dextrose brain broth Course of the infection in inoculated animals was followed by daily examination of thick smears of tail blood in Giemsa s stain

Penicillin was started 22 hours after inoculation and continued four days Subcutaneous injections of 125 Oxford units of *sodium penicillin in 0 1 cc physiologic* salt solution were administered five times daily and 500 units of powdered sodium penicillin suspended in sesame oil was given to last the night Most mice appeared some

(3) P oc. Staff Meet M yo Cl n. 18 457 467 Dec. 1 1943

excreted rapidly in the urine so that to obtain an adequate amount of potent material in the circulating blood and tissues it is necessary to inject penicillin continuously or at frequent intervals i e every three to four hours The average patient requiring intravenous or intramuscular injections for serious staphylococcic infections requires a total of between 500 000 and 1 000 000 Oxford units and the best results have been observed when treatment is continued for at least 10–14 days At least 10 000 units should be given every two to three hours at the beginning of treatment either by continuous intravenous injection or by interrupted intravenous or intramuscular injections

Patients with pneumococcic pneumonia frequently recover following administration of 100 000 units given over a three day period This is especially important in sulfonamide resistant pneumococcic infections It may be necessary to give between 60 000 and 90 000 units daily for four to seven days to achieve maximal effect

In treatment of empyema or meningitis it is advisable to use penicillin topically by injecting it directly into the pleural cavity or the subarachnoid space

Toxic effects are rare Occasional chills with fever or headache and flushing of the face have been noted Urticaria has been reported and thrombophlebitis at the site of injection has been described

Penicillin in Treatment of Osteomyelitis and Other Infections M A Pittman (Wilson N C) reports a case of acute osteomyelitis treated with penicillin

Boy 11 was admitted with severe pain in the region of the right femur high fever and inability to walk of four days duration Two weeks previously he had had a small furuncle above the right knee Temperature was 106 F pulse 130 leukocyte count 16 000 per cu. mm Roentgenograms of the femur disclosed no pathologic process Tentative diagnosis was osteomyelitis

Sulfathiazole therapy was instituted but this was without effect. Fever continued and roentgenograms on the fourteenth day showed degenerative changes of the upper and lower

(6) V gi ia M M thly 71 66-70 F bru ry 1944

infections Mice were used in the toxoplasma experiments and the treated mice died in the same interval as the infected untreated controls

Eleven mice were inoculated intraperitoneally with 0 25 cc heparinized pooled blood from five mice showing heavy infections with relapsing fever (Spirochaeta novyi) Twenty four hours later the infections were moderately heavy and treatment of six of the mice was started with penicillin sodium The first dose was 1 000 units in 1 cc saline intraperitoneally Every 3 hours thereafter for 48 hours each treated animal received 500 units total dose being 9 000 units First effects of the drug were observed six hours after the first dose The infections had decreased in intensity to about one fortieth in the treated mice whereas they had increased about 50 per cent in the controls After 27 hours no spirochetes were microscopically visible in the treated mice whereas in the controls they averaged 140 in a single oil immersion field Sixty hours after treatment was begun two apparently cured mice were killed and citrated heart blood of each was inoculated intraperitoneally into two new mice No infections resulted In a second experiment a mouse with relapsing fever killed after receiving 4 000 units in 19 hours was found to be a carrier though no spirochetes were found in a thick drop of its blood

Penicillin in Treatment of Infections Based on a study of 500 patients with infections treated with penicillin the Committee on Chemotherapeutic Agents of the National Research Council presents its conclusions

Penicillin has been found to be most effective in treatment of staphylococcic gonococcic pneumococcic and hemolytic streptococcic infections It has been disappointing in treatment of bacterial endocarditis Its effect is particularly striking in sulfonamide resistant gonococcic infections following injection of 100 000-160 000 units over a 48 hour period

Following intravenous or intramuscular injection it is

(5) J A M A 122 1217 1224 Aug 28 1943

GENERAL CONSIDERATIONS

Initial Aerobic Flora of New Born (Premature) Infants Nature, Source and Relation to Ultraviolet Irradiation and Face Masks There is general agreement as to bacterial types constituting the basal flora in the upper respiratory tract of new born infants but difference of opinion as to their derivation and presence of such pathogens as the beta hemolytic streptococci pneumococci and influenza bacillus To clarify the latter point and to determine more definitely the sources of initial flora and modes of transmission to the respiratory tract John C Torrey and Martha K Reese[8] (New York City) made cultures from nasopharynx and throat of over 150 prematures

The initial aerobic bacterial flora of the throat and nasopharynx of artificially fed new born infants is largely acquired through direct contact with adults and not from the parturient canal as claimed by Witkowski and others The principal vehicle of transfer is droplets of saliva The flora in premature infants is essentially the same as that reported by Kneeland for full term infants

Although occasional contact with adult carriers of pathogens such as pneumococci Haemophilus influenzae and beta hemolytic streptococci occurred the first two organisms were not present and hemolytic streptococci rarely present That only one or two of the five or more fermentative types of nonhemolytic streptococci primarily implanted were able to persist suggests that apparent absence of these pathogens may be due to failure of adjustment of the micro organism to the immature mucous membrane rather than to presence of specific immunologic factors Up to 16 hours after birth the nasopharynx and throat of about 80 per cent of 16 infants exhibited sterility with the cultural methods used From 24 to 48 hours after birth 50 per cent of 12 infants in wards exposed to ultraviolet

(8) Am J D Child 67 89 99 February 1944

thirds of the right femur The nineteenth day penicillin therapy was begun 20 000 units was given intravenously the first day followed the next day by 40 000 units On the fourth fifth and sixth days of penicillin treatment temperature did not exceed 100 F and on the succeeding three days did not go above 99 F Thereafter the temperature was normal Beginning the fourth day penicillin was given intramuscularly 10 000 units every four hours

The boy remained afebrile in the two months subsequent to discharge Roentgenograms disclosed new bone formation in the femur and recovery seemed certain

Extraction of Highly Potent Penicillin Inactivator from Penicillin Resistant Staphylococci William M M Kirby (Stanford Univ) used seven strains of Staphylococcus aureus (coagulase positive) naturally penicillin resistant but isolated from patients who had not received penicillin to prepare a penicillin inactivator using Harper s method of extraction

Saline suspensions of 24 hour plate cultures were precipitated with 7 volumes of acetone After a change of acetone and two of ether the precipitate was dried quickly in vacuo and stored at room temperature Complete destruction of 100 units of penicillin by 1 mg of the powder was so rapid that at the end of 12 hours growth in the tube was equal to that of the control Although there was some variation high potency was shown by extracts of all seven strains Extracts of seven penicillin sensitive strains of Staphylococcus aureus (coagulase positive) were tested the same way using 2 mg powder and only 1 unit of penicillin and in no instance was there inactivation of penicillin

Actively growing cultures of the resistant strains caused complete destruction of penicillin in the culture fluid but the Seitz filtrate of the fluid contained no penicillin inactivator Ability to destroy penicillin was completely lost when a broth suspension of the powder was left at 56 C for one hour

(7) Sci n e 99 45 453 J 2 1944

pig skin general intoxication of mice and in vitro tests yielded identical results in every instance in the series

The toxin of Clostridium welchii D is resistant to this mechanism but subject to detoxication by a system consisting of manganese plus hydrogen peroxide staphylococcic and Clostridium welchii A toxins can be detoxified by both Iron is more active in an intoxication in which the toxin reacts slowly with the tissues manganese is more active when toxin reacts more quickly Although Walbum s explanation seems to be erroneous the authors agree with his general conclusions that different metals are active in different infections and toxic states He found manganese active in antitoxin production beryllium in agglutinin production cesium and iridium in mouse typhoid infections and aluminum manganese and gold in guinea pig tuberculosis In intoxication of rabbits with staphylococcic diphtheria or dysentery toxin best results were obtained with manganese

Since toxin is detoxified in the organs and not in blood and since iron as cytochrome was more active than as hemoglobin or ferritine it appears that metal proteins which determine resistance against infectious diseases and intoxications are constituents of organ cells Investigations will have to determine the metal protein or proteins most severely affected in infectious diseases Iron alone will probably not be effective in maintaining resistance to infectious diseases since it has been shown that it is insufficient to restore normal enzymatic activity of depleted organs Activity of metals is not restricted to bacterial intoxication but extends to other toxemic states It has long been known that anaphylactic shock can be prevented by manganese ascorbic acid sodium thiosulfate or cysteine In preliminary experiments it was found that iron can prevent local anaphylactic reactions in guinea pig skin that iron and copper reduce the intradermal tuberculin reaction in tuberculous cows and that iron and manganese reduce the reaction following a Mantoux test in humans These experiments indicate that the detoxication mecha

irradiation still showed sterility as contrasted with 12 per cent of 16 infants in wards not so irradiated Beyond that time results for the two groups were essentially alike except for hemolytic Staphylococcus aureus Ultraviolet irradiation did not retard the acquisition of nonhemolytic streptococci but did delay infection with hemolytic strains of Staphylococcus aureus

Ultraviolet irradiation as applied does not prevent person to-person transmission of pathogens through the air within the range of a few feet Among infants 7–25 days old in wards without ultraviolet irradiation 60 per cent were carriers of hemolytic strains of Staphylococcus aureus in the nasopharynx Of 98 strains tested for presence of coagulase 86 per cent gave positive results and thus presumably were potential pathogens

Strains of streptococci and of Staphylococcus aureus normally present in the throat and nasal passage of adults passed to some extent through the face masks worn even in absence of coughing and sneezing Acquisition of hemolytic strains of Staphylococcus aureus was highest in the late winter and spring months and lowest in the early fall

Action of Metals on Bacterial Intoxication. In studies on diphtheria staphylococcic and Clostridium welchii A and D toxins Mary H Petherick and E Singer (Melbourne) demonstrated a detoxication mechanism which operates by combined action of metal compounds and either redox substances or hydrogen peroxide Of numerous iron compounds tested with diphtheria toxin those containing iron in ionized form showed highest activity Metal protein combinations may be more active than inorganic salts as inorganic salts are more active when dissolved in serum than when dissolved in broth or saline Detoxication might be an oxidative process the toxin molecule being directly oxidized by activated oxygen components of the detoxication system varying with different toxins Iron copper and zinc and ascorbic acid glutathione and adrenalin are most active with diphtheria toxin Experiments with guinea

(9) A stral J Exper Biol. 22 21 27 M ch 1944

and tripled after 2-3 days the second injection should not be given more than 10 days after the first The same dose may be given subcutaneously

Two days before injection the serum is diluted in sterile physiologic saline (1 10) poured into ampules sealed and stored in the refrigerator (+4 C) Its sterility is checked by inoculating broth and agar agar Before injection the solution is heated to 37 C in warm water and is introduced into the vein very slowly If the ampule shows traces of sedimentation the serum is not used

On the basis of over 2 500 clinical observations presented at the conference the therapeutic effect of antireticular cytotoxic serum was clearly established in war traumatisms and the following diseases (1) frost bite and wounds (reported by B E Linberg) including open closed and especially slowly knitting bone fractures slowly healing sluggishly granulating and infected wounds general purulent infections purulent inflammations of cavities and tissues frost bite and burns of second and third degree infected traumatism of the eye (2) infectious diseases including spotted typhus puerperal and gynecologic sepsis rheumatism unresolved pneumonia and lung abscesses and tonsillitis (3) diseases of the nervous system especially traumatic and infectious diseases such as neuritis meningo encephalitis disseminated sclerosis and psychoses (4) diseases connected with disordered trophic function such as duodenal and gastric ulcers ozena and eczema

Effect of cytotoxic serum on spotted typhus is particularly striking The disease is definitely made milder and the temperature lower and the dreaded complications of the nervous and cardiovascular systems which usually occur on the tenth or eleventh day are fewer The disease is also hortened by three or four days The serum should be used on the fifth or sixth day because later cardiovascular changes occur

In infectious diseases stimulating doses of serum will produce best effects if used during the second (allergic)

(4) Sov t m d n 1 pp 4 5 1943 Am R So t M d 1 1 4 1 7 D embe 1943

nism is active in a wide range of toxemic conditions and furnish a rational basis for the fact that resistance against infectious diseases is lowered by malnutrition

Therapeutic Action of Antireticular Cytotoxic Serum Several reports are presented of a conference on this subject by physicians of the U S S R[1]

Antireticular cytotoxic serum proposed by Alexander A Bogomolets is a powerful specific factor influencing the physiologic system of the connective tissue and exerting a strong stimulative action on cellular elements of the system if used in small doses as established by experimental investigations and clinical observations Since connective tissue has important trophic and protective functions use of the serum is recommended in treatment of various diseases connected with a weakening or inhibition of these functions

Reactivity of the physiologic system of connective tissue may be determined by numerous tests in addition to clinical observations The following tests are recommended for this purpose (1) dermal test with trypan blue (2) morphologic study of the blood (3) determination of sedimentation rate of erythrocytes (4) determination of titer of complement opsonic index and phagocytic activity of leukocytes and (5) dermal test with antireticular cytotoxic serum

A method of preparing antireticular cytotoxic serum is described by P D Marchuk[2] which consists of immunizing animals with antigen of human spleen and marrow The serum is suitable for use when the titer of cytotoxins determined by complement fixation is not less than 1 100 and the hemolytic titer not higher than 1 16 It is used only in a 1 10 *solution of physiologic saline The stimulating dose is* 0 1–0 25 cc for an adult The dose may be increased to 0 3 cc depending on weight and condition of the patient For intravenous injection the dose of serum solution (1 10) is 1–2 5 cc Injection may be repeated

(1) Am Rev Sovi t Med. 1 101 129 Dec mber 1943
(2) Ib d. pp 101 112
(3) J med. Acad. d sc de la RSS d Ukra ne 9 1175 1189 1939 Am. Rev Sov t Med 1 113 123 Dec mbe 1943

ever the paucity of data reported on finished waters precludes a definitive conclusion regarding the utility of L S T broth in examination of this important group of waters

The use of the confirmed test (transfer of primary gas positive to brilliant green bile taking gas in the latter to indicate the presence of coliform organisms) yielded about as many positive results as did any of the completed tests whether transfer was made from the lactose broth or the L S T broth primary gas positives Transfer from the L S T broth however resulted in a small increase (3 8 per cent) in the number of positive confirmed tests compared with transfer from lactose broth gas positives

Substitution of lauryl sulfate tryptose broth for lactose broth in the Standard Methods procedures promises reduction in the number of primary gas positives to be confirmed and an increase in the number of positive indications of the presence of coliform organisms Further study of the medium is recommended

Effect of Alcoholic Intoxication on Acquired Resistance to Pneumococcic Infection in Rabbits is reported by Clarence C Lushbaugh (Univ of Chicago) The study was undertaken to determine (1) how alcoholic intoxication might influence mechanisms of active immunity and (2) to what extent large amounts of antibody might tend to counteract loss of resistance caused by alcohol Of 120 rabbits used 56 were actively and 20 passively immunized 44 were nonimmune All except 22 nonimmune animals were infected at the beginning of the experiment These 22 were given the same amount of alcohol as the infected animals to determine whether that amount or the technic used would cause death Alcohol was given in intoxicating doses to 34 actively immunized and to 15 passively immunized animals in addition to the 22 mentioned

Alcoholic intoxication lowers resistance to infection in that rabbits whether actively or passively immunized against type I pneumococci died with septicemia after dermal infection with pneumococci of the same strain

(6) J Imm l. 46 151 162 M h 1943

period of their course In the acute rheumatic process a single injection may stop progress of the disease The serum is contraindicated in patients with myocarditis and exact dosages must be further investigated

[Some confirmatory work would seem especially desirable before evaluating this work—Ed]

Practical Study of Lauryl Sulfate Tryptose Broth for Detection of Presence of Coliform Organisms in Water Mac H McCrady[3] (Montreal) reports a study in which 17 laboratories collaborated. A total of 605 water samples from which primary gas positives were obtained were examined with L S T broth as a primary and as a secondary medium for comparison with lactose broth in the completed test procedure adopted by the Standard Methods Committee on Water and Sewage Of these 526 were also subjected to the confirmed test procedure employing transfer from lactose broth primary gas positives to brilliant green bile 318 were examined further by transfer from L S T broth primary gas positives to brilliant green bile

A reduction of about 13 per cent in the number of sample portions producing gas in the primary medium resulted when L S T broth was substituted for lactose broth this reduction being particularly evident in the results from unfinished finished and swimming pool waters

As coliform organisms were isolated from only 75 1 per cent of L S T broth primary gas positives when using lactose broth secondary and from 77 5 per cent when using L S T broth secondary in the usual Standard Methods completed test procedure it is evident that L S T broth could not be used as a presumptive medium without confirmation in examination of these waters

Since use of L S T broth as both primary and secondary mediums permitted isolation of coliform organisms from 1,261 sample portions about 13 per cent more than the 1 171 portions from which isolations were secured when lactose broth was employed substitution of the former medium for the latter appeared to be advantageous how

(3) Am J P h He lth 33 1199 1 07 Octob 1943

by both trigeminal and olfactory pathways Demonstration that the strain of herpes virus used in these experiments is encephalitogenic that in suckling mice it reaches the brain from the nasal mucosa by neural routes and that it is able to utilize the olfactory pathways adds considerable significance to the finding that a purely humoral immunity is capable of protecting mice of this age against virus given by this route Experiments to determine whether mice can be passively protected against viruses which pursue the olfactory pathway exclusively are under way

It was also considered desirable to study the extra neural lesions of herpetic infections Studies disclosed that intranasal instillation of herpes virus in suckling mice re sults in specific lesions widely distributed in the viscera The lungs are infected by aspiration of the virus Virus disseminated by way of the blood establishes itself in endothelium in certain situations where parenchymal le sions result by direct spread from the vascular foci Evi dence of blood borne infection was found frequently in the liver and spleen less frequently in the adrenals and in one instance in the bone marrow Renal infection appeared to be uriniferous Lymph carriage of the virus also occurs and lymph nodes draining infected areas were often found to contain herpetic inclusion bodies Herpes virus seems incapable of invading the central nervous sys tem of suckling mice by the vascular route

Diagrammatic Representation of Human Blood Group Reactions Alexander S Wiener and Harris E Karowe (New York City) offer a pictorial representation of the blood group factors and reactions based on the newer knowledge of antigen antibody reactions in general which helps not only to visualize the specificity of combinations but also to explain the reactions of for example the so called anti O serums as well as certain differences in the behavior of the group substances in the cells and in secre tions

The blood group hapten can be visualized as having a certain basic structure probably polysaccharide In group

(8) J Imm nol. 49 51 61 July 1944

Alcoholic intoxication reduces resistance by inhibiting rapid mobilization of the local inflammatory response con sequently micro organisms multiply too rapidly for the reduced number of leukocytes entering the infected site to destroy them even in the presence of active immunity except where this immunity is unusually high

Lowered resistance of infected rabbits intoxicated with alcohol can be bolstered with large amounts of specific antibody This is seen in survival of actively immunized animals with high titers and one passively immunized animal that received five times the amount of antibody needed to protect a normal animal This greater amount of antibody probably holds the infection localized long enough for the sluggish tissue defenses to mobilize and thus is the deciding factor in intoxicated immune animals' resistance to infection

[That alcohol lowers resistance to infectious processes has been demonstrated many times but it cannot be too much empha sized —Ed]

Studies on Herpetic Infection in Mice are presented by George Packer Berry and Howard B Slavin[7] (Univ of Rochester) Initial studies were concerned with the nature and mode of acquisition of the immunity exhibited by mice born of immune mothers It was found that passive immunity naturally acquired from immune mothers or arti ficially induced through administration of immune rabbit serum conferred on suckling mice of the albino Swiss strain a high degree of resistance against herpetic infec tion following intranasal instillation of the virus Anti bodies which could be readily demonstrated in the blood of 2 week old mice were received by the offspring of immune mothers primarily by the mammary route Natur ally acquired immunity declined rapidly when suckling was interrupted Herpes virus was not recovered from the fetuses of either immune or infected nonimmune mothers

Instilled intranasally into suckling mice a mouse passaged strain of herpes virus (HF) reaches the brain

(7) J Exper Med. 78 305 326 October 1943

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Instilled intranasally into suckling mice a mouse passaged strain of herpes virus (HΓ) reaches the brain

(7) J Exper Med. 78 305 326 October 1943

In group AB it is assumed that there is only a single type of molecule with two different polar groups A and B respectively rather than a mixture of two kinds of molecules (Fig 1) It is further assumed that in the red cells these haptens are combined with lipids or lipoproteins while in the secretions they occur free in molecular form or in relatively small molecular aggregates

If as in other antibodies the natural or immune isoagglutinins as well as the immune anti A and anti B agglutinins produced in animals are modified serum globulins the specificity of the reaction can be explained in the following manner The active patches on the anti A globulin molecules are considered to have a configuration that conforms with the arrangement of the polar groups on the A haptens and in a similar way the essential portion of the anti B agglutinin would be the counterpart of the B hapten Thus as shown in Figure 2 it can be readily visualized how for example the anti B agglutinin combines with the B agglutinogen and why it does not react with group O or group A blood



F g 2 — Spec fi combination between B aggl t noge d ti B aggl ti in Sh w ttr ct on between p l g oups Show st t fer

The fact that two serums of equal titer may differ considerably in avidity can be explained by the assumption that there exists a practically unlimited number of variations of anti B and anti A agglutinins The titer merely measures the concentration of antibody whereas the avidity reflects its quality The avidity of the combination between agglutinogen and agglutinin should be considered to depend not only on the polar groups involved in the reaction but also on apparently indifferent groups which by steric interference may reduce the firmness of the union The subgroups of groups A and AB can be visualized as

O (genotype OO) only this rudimentary structure with its rather weak polar groups may be assumed *to be* present Agglutinogen A will be conceived to have the basic structure plus a certain relatively complex strongly polar

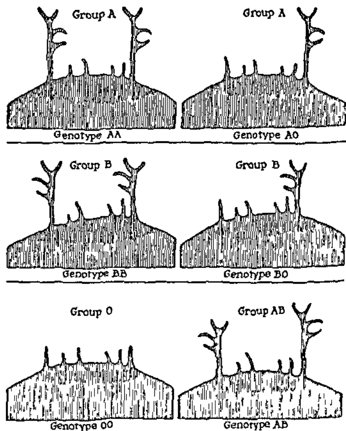


Fig 1.—Aggl ti gens of four blood groups

group, in genotype AO only one such group would be present in the molecule while in genotype AA the polar group is supposed to be duplicated at each end of the hapten Agglutinogen B is represented in a similar way with the aid of a different polar group of

DISEASES OF THE CHEST
(EXCEPTING THE HEART)

J BURNS AMBERSON M D

dependent on the existence of more than one sort of polar group capable of combining with anti A antibodies The easiest way to represent the subgroups is by considering the polar group A_2 to be very similar to but slightly shorter than polar group A_1 in the rare agglutinogen A_3 the polar group is represented as still shorter

If it is postulated that anti O agglutinins combine with that portion of the blood group hapten common to human bloods of all groups then the peculiar behavior of the anti O serums (they react regularly and not quite as intensely with A blood agglutinate occasional A_1 and B bloods and hardly react with A_1B blood) can be explained with the aid of the diagrams of the hypothetical group antigens shown in Figure 1

Quantitative studies of the group substances in saliva and other secretions by the inhibition technic have confirmed the specificity of the properties A and B with certain limitations While the difference between A and B in secretion is as pronounced as in blood such is not the case for the subgroups of A or in tests carried out with anti O serums Saliva from individuals of subgroups A_1 and A_2 can hardly be distinguished in either qualitative or quantitative tests with the exception that saliva from A B individuals has a somewhat lower inhibitive titer Salivas of all groups inhibit the anti O agglutinins To explain these observations it is assumed that the group substances outside the erythrocytes are free so that the polar groups A and B are less rigidly fixed in position Thus if the A and B polar groups of the group AB substance in secretions can bend outward the anti O serum could combine with it This would demonstrate that the so-called group O substance is not determined by a recessive gene but is part of the structure of the group substance of all groups as concluded by Witebsky and Klendshoj On the other hand the steric interference caused by the postulated more rigid arrangement of the polar groups on the erythrocyte would explain the correlation between the genotype and the reaction of the blood

PART II

DISEASES OF THE CHEST

MICROSCOPIC ANATOMY OF THE LUNGS—NORMAL AND ABNORMAL

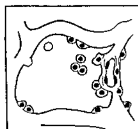
Contribution to Study of Lymphoid Formations in the Normal Human Lung A review of the literature on histology of the human lung reveals that some authors do not mention any lymphoid tissue in their minute descriptions of lung parenchyma Others speak of their presence but do not substantiate their claims by accompanying photomicrographs Still others deny the original presence of lymphoid tissue in the pulmonary parenchyma stating that its subsequent appearance is caused by stimuli derived from the air and blood

Because of the constancy with which adult lungs even normal ones harbor foreign particles especially of the carbon variety which may stimulate a cellular reaction Tomas G Perrin (Univ of Mexico) studied lungs removed from two new born infants who breathed only shortly after birth and who died as a result of obstetric intervention The lung sections were carefully arranged topographically and regional studies were made of each pulmonary lobe and its subdivisions into upper middle and lower portions as well as in superficial and deep zones The lymphoid formations encountered in these lungs were of three categories (1) diffuse not well delimited lymphocytic accumulations with little supportive tissue i e lymphocytic infiltrations (2) lymphocytic groupings provisionally designated as prenodules showing a tendency to nodule formation by the interrelationship of histiocytes

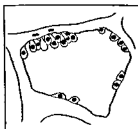
(1) M d na M 3 46 49 N 23 1

presence of lymphoid tissue in the lung has considerable significance in many diseases —Ed]

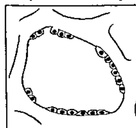
Pulmonary Alveolar Lining under Various Pathologic Conditions in Man and Animals is described by E F Geever K T Neubuerger and C L Davis (Denver) The human material was selected from 4 000 autopsies No evidence of continuous alveolar epithelium was observed in normal adult lungs only occasional scattered



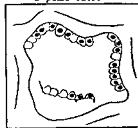
Septal Cell Sw ll ng



Rapid M b l zat on— S ptal Cells



Low Cubo dal L n ng



H gh Cubo dal L n ng

F g 3—R p t t t g ptal ll ct ty

septal cells were seen Epithelium like lining cells were found in various pathologic conditions delayed resolution and organization of lobar or bronchopneumonia lobar pneumonia associated with other conditions virus pneumonia and lipoid pneumonia Septal proliferation and alveolar lining were found in one case after irradiation for a bronchial tumor Active tuberculous foci commonly

( ) Am J P th 19 913 93 N mb 1943

lymphocytes and few lymphoblasts and a reticulum poor in precollagen (3) *encapsulated lymphatic follicles* i e true lymphoid organs with double collagenous and pre collagenous stroma and with histiocytic lymphocytic and lymphoblastic parenchyma in close correlation with blood vessels The lymphocytic infiltrations and prenodules the latter measuring 125–280 microns were encountered in the peribronchial connective tissue and adventitia of the bronchioles occasionally at the point of their bifurcation The larger nodes (0 5–8 mm in diameter) were seen in the vicinity of the venules more often of the arterioles which were occasionally enveloped by the lymphoid structures *the arrangement reminiscent of that in the malpighian* bodies of the spleen The regional distribution of the lymphoid tissue in the various lobes and their subdivisions showed no systematization Whereas the middle lobe of the right lung of the first infant showed no trace of lymphatic formations that of the second infant presented all three aforementioned types but there was no capsule formation in the lymph follicles or any evident relationship to the blood vessels

The cellular formations found by Guieysse Pellissier in rabbits and dogs and designated by him as nests of nuclei *and giant nuclei were not encountered in this study of* human lungs

Perrin concludes that chronic infectious processes and pneumoconioses far from inducing the formation of lym phatic nodules in the lung as maintained by various workers produce sclerosis in the originally existing ones Examination of hundreds of cases of pulmonary tubercu losis silicosis and anthracosis existing singly or in com bination revealed that none showed such complete and active lymphoid formations as are seen in the lungs of new borns Moreover the hyperplasia noted in such cases in a few intrapulmonary lymph follicles involves the his tiocytic elements while the lymphoblastic elements are markedly destroyed

[This study tends to confirm the work of other anatomists The

brings about thickening of the interalveolar septums with displacement of the capillaries away from the surface and consequent loss of respiratory function the alveolar epithelium may undergo hyperplasia to form a continuous epithelial lining The cells are either cuboidal or columnar and some of them may secrete mucin There is convincing evidence that the epithelium forms locally and does not



Fg 5 (l ft) —A f sol d t d l g Al l all l ed by b al l mna p thel m. H m to yl n d d f m × 60

Fg 6 (ght) —S m der h gh m gn ficat Th k ng f s ptum d e h fly to p th l al l y H m t xyl d d f m × 100

grow from the bronchi In chronic passive congestion and interstitial pneumonia epithelization of the alveoli follows thickening of the interalveolar septums Mild irritation of the alveolar walls by foreign bodies may bring about epithelization as in lipoid pneumonia

In man two examples of widespread epithelization similar to jagziekte in sheep have been observed These may be regarded as cases of diffuse epithelial hyperplasia due to an unknown irritant One case was reported by Bonne

exhibited perifocal septal cell proliferation and alveolar lining formation similar changes but to a lesser degree were found surrounding a syphilitic gumma of the lungs In alveolar cell tumors which in the authors opinion arise from septal cells and are entirely independent of the bronchial system the alveoli are lined by cuboidal or columnar anaplastic cells with papillary protusions Septal cell proliferation is commonly found around silicotic nodules and occasionally around pulmonary infarcts scars abscess or gangrene

Figures 3 and 4 show stages of alveolar lining formation from simple swelling of septal cells to formation of a continuous epithelioid lining and to actual neoplastic growth (alveolar cell tumor) Lining formation is found more frequently in certain regions of the lung such as *those subjacent to the visceral* pleura along the interlobular septa and in perivascular and peribronchial areas Differentiation between septal cell proliferation and bronchial epithelial downgrowth into the alveolar ducts and alveoli is important The squamous type of downgrowth can be readily identified Columnar bronchiogenic downgrowth is high columnar in type the nuclei are oval or rodlike and the lumen of such spaces does not contain as many mononuclear phago*cytes as do zones of septal cell proliferation*

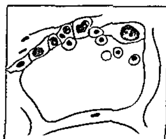


Fig 4—Stage in septal cell activity

Histologic observations indicate that the proliferative process leading to the formation of alveolar lining occurs within the mesenchymal tissue of the alveolar wall

Hyperplasia of Pulmonary Alveolar Epithelium in Disease In the postnatal lung the alveolar walls are formed *almost entirely* by the capillaries but a few epithelial cells persist in the niches between them In any disease which

nimes respirating surface Furthermore because of its metabolic function respiration is closely linked to circulation Efficient respiration is inconceivable without a quan

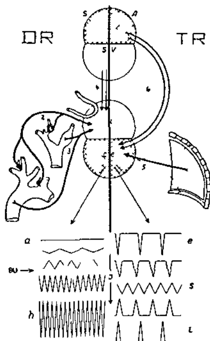


Fig 7—S h m t p t t f g l t ry m h m f th resp t y t E t gul t on th l ft (sp t y d b t *DR*) d t egul t n th ght (p t ry typ *TR*) 1 the upper p rt f th d g m d t p rat ry t t t ff to ce t *SV* g tati y t m *SA* m l ou y tem 1 entral hem cal p d ct t l (b d d) efl x h m l ont ol (ca bon d l d l k f yg) 3 fl t l f h m dynam rigin (d t l te) 4 t l rv t l (g tat) 5 flex p p ept t l (p lm nary d te t) 6 entr l n rv cont l of type f p at n. Low p rt f th figu h w co spo d g ff cts on th p m g m J m t t w d th b ttom p p h hype p p at ry typ ymm trical typ nsp tory type.

titative relationship between ventilation and pulmonary surface and the circulation

Controls of metabolic origin proprioceptive and cir

in 1939 The other is reported by E T Bell (Univ of Minnesota) Neither justifies interpretation of neoplasm

Man 63 complained of dyspnea on exertion productive cough weakness and loss of weight for two years Physical examination revealed consolidation of the left lower and right middle lobes Introduction of lipiodol revealed an unusual appearance of the small bronchi in that they showed diffuse narrowing Tentative diagnosis was carcinoma of the lung The patient died elsewhere Macroscopic examination of the lungs indicated diffuse consolidation Microscopically every alveolus was seen to be lined by cubical or columnar epithelium (Figs 5 and 6) Interalveolar septums were moderately increased in thickness due chiefly to the epithelial layers and not to leukocytic infiltration and fibrosis as in interstitial pneumonia The septums were not destroyed by epithelial invasion as in carcinoma

[The two preceding articles present conceptions which may help to explain pulmonary dysfunction and failure and the resulting picture of cor pulmonale The disabling effects may be long developing Prevention obviously consists of adequate treatment of the initial disease —Ed]

RESPIRATORY FUNCTION

Regulation of Respiratory Motor Activity Oscar A M Wyss states that ventilatory movements of the respiratory apparatus require in man energy representing 0 1 per cent of total energy metabolism Such consumption of energy necessitates a regulatory mechanism automatically adapting intensity and frequency of movements to metabolic needs (Fig 7) The motor function of the respiratory apparatus consists of rhythmic movement of a portion of the skeletal muscles and is subject to proprioceptive auto regulation of the whole motor system Reflex control mechanisms which adapt general posture and movement to variable mechanical conditions of the muscular system are no less important for functions related to position and movement of respiratory organs Two fundamental factors regulate gaseous exchange in the lungs movement which assures pulmonary ventilation and position which deter

(3) Am J Path 19 901 911 November 1943
(4) Schweiz. med Wchnsch 73 961 965 Aug 7 1943

(apnea) Elevation of carbon dioxide tension increases the central stimulation and results in dyspnea

[The complexity of respiratory regulation is gradually being elucidated by such physiologic studi as thi The concepts are of basic importance for the understanding of many clinical pictures and for the proper management of functi nal disturbances —Ed]

Analysis of Breathing Pattern Relatively little attention has been accorded the fact that healthy persons vary greatly in their manner of breathing (Fig 8) J L Caughey Jr[5] (Columbia Univ) presents a method for studying spirograms with the hope that this kind of analysis will provide material for correlation with other aspects of the total personality of the individual Spirographic records of 500 female and 200 male patients were studied with repeated tests records numbered 704 and 280 respectively Persons under 16 and patients with obvious cardiac or pulmonary insufficiency were excluded the group represents a cross section of adult patients sent for basal metabolism tests Vital capacity of women is close to 2 000 cc per sq M body surface while that of men is approximately 2 500 cc A chance relationship between these figures and construction of the Benedict Roth apparatus used facilitated expression of ventilatory volumes on these spirograms in terms of the person s estimated vital capacity Factors considered in study of the spirograms were calculation of total breaths and total inspired volume rate of breathing depth of breathing volume of ventilation expiratory pause sighs sighing increment swallowing individual variation variation in depth of breathing expiratory position inverted contour rapid expiration and general irregularity On a spirogram the decreasing speed of expiration is shown by gradual rounding of the contour during the latter part of expiration (Fig 8 *A*) when there is no expiratory pau e change from expiration to inspiration is represented by a sharp point like that normally found at transition between inspiration and expiration (Fig 8 *B*) in some records a long delay is present between successive breaths (Fig 8 *C*)

(5) Am R T b 48 38 40 D mb 1943

culatory represent automatic respiratory regulation This permits constant adaptation of respiratory movement to metabolic needs of tissues through mechanical factors which intervene in respiratory activity Metabolic needs demand that a certain quantity of air pass through the lungs within a certain time This represents the respiratory debit or pulmonary ventilation In addition mechanics of the respiratory apparatus allow adoption of a type of respiration effective in varying rate of movements as well as position of the lungs Consequently the body can maintain the same ventilation in different ways by adapting the type of respiration to mechanical circumstances

Function of respiration is regulated through the automatic respiratory nerve center and is subject to influence of humoral regulators The nerve center has two distinct functions although these are influenced by each other One is the primary initiating center of autonomous rhythmic activity and there is a secondary co-ordinator dependent on the former All influences proceeding from metabolic needs necessarily exert their effect on the respiratory initiator which controls pulmonary ventilation All afferent impulses concerned with type of respiration involve the effector or co ordinating center i e factors influencing automatic activity of the primary center represent extrinsic regulation and direct effects on the internal nerve mechanism of the effector center constitute intrinsic regulation

Among various mechanisms involved in extrinsic regulation of respiration lack of oxygen or excess of carbon dioxide are of first importance There is great variation in ventilatory activity with slight change in the level of carbon dioxide in inspired air which indicates *that elimination of* carbon dioxide is even more important than oxygen supply Carbon dioxide in the blood acts directly on neurons of the initiator center modifying the intracellular reaction *(pH) Diminution* of carbon dioxide decreases central stimulation and consequently pulmonary ventilation this can lead to complete suppression of respiratory movements

system (2) stigmas of voluntary or subconscious interference with this mechanism produced by higher brain centers in response to purely emotional or nervous stimuli These ventilatory but not truly respiratory portions of breathing behavior are of many types Because breathing is so easily affected by cerebral controls these variations must be interpreted cautiously But frequent sighs marked lability of ventilatory mechanics gross distortion of breath contours and inability to maintain an even expiratory position are important signs of constitutional instability comparable to instabilities frequently observed in heart rate blood pressure peripheral blood flow and intestinal motility This lack of correlation between basic respiratory needs and breathing behavior imposed by cerebral influence over the autonomic mechanism lies behind the clinical problem of hyperventilation The natural reaction of any individual who senses some interference with air intake is to fight for more breath voluntarily and with muscular effort gaged to the supposed seriousness of the situation When the sense of insufficient air intake arises from some normal stimulus such as increased use of oxygen during physical exertion the breathing effort serves a useful purpose If however the sense of inadequate ventilation arises from a source other than respiratory needs the voluntary breathing effort serves only to remove carbon dioxide in excessive amounts setting the stage for alkalosis Common situations in which this nonrespiratory stimulus to over ventilation may appear are substernal pressure of coronary insufficiency left chest discomfort of patients with cardio vascular neurosis and the uncomfortable thoracic sensation following a sigh which though deep has not attained a sufficient inspiratory peak to give satisfactory muscular relaxation at the end of expiration

The untrained subject when fighting for breath concentrates on an increase in rate and depth of inspiration This leads to progressive difficulty in attaining satisfactory emptying of the lungs during expiration since little time is left for this part of the respiratory cycle In the spiro

Breathing patterns furnish graphic evidences of conflict between two fundamental biologic processes (1) rhythm produced by respiratory needs acting through chemical and physical channels and expressed by the autonomic nervous

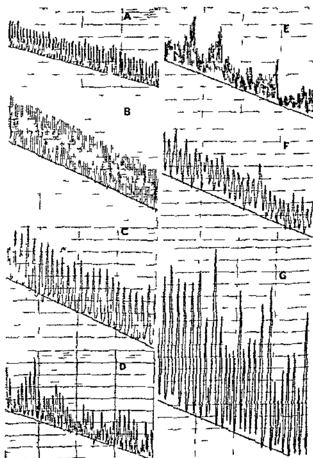


Fig 8—Differences in breathing beh of p tents und basal co d t o s B n dict Poth m tabol m app at w used E h sp g m beg s at lower ght corne n p ration e o d d by a cend g l ne expi at on by d s nd ng l e. Horizontal ruled l p at d by 2 mm. qu lent to mo eme t f 41 4 cc g s i 0 o t f m h e Vertical ruled l nes sep ated by d ta ce th ough wh h kym g aph m es n o min te

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gram evidences of this kind of breathing stand out in the finding of a large volume of ventilation and in marked and sustained elevations of expiratory position These are often accompanied by disappearance of expiratory pause and increased breathing rate Clinically appearance of many sighs on a spirogram indicate emotional or neuromuscular tension The chief respiratory problem they suggest is not hypoventilation anoxemia but hyperventilation alkalosis especially if frequent or superimposed on an already large volume of air intake

Since the metabolism test is based on the slope of the line drawn along the expiratory points of the patient s spirogram it follows that if breathing performance during the test is uneven particularly if there are alterations in volume of air in the lungs at the end of expiration there is no possible way to derive an accurate measurement of basal metabolic rate Sound clinical practice demands that the physician familiarize himself with a satisfactory breathing pattern and refuse to accept any report of basal metabolism not based on an adequate spirogram

As an initial step in defining some characteristics of an average spirogram Caughey presents the following average rate—women 11–18 per minute men 9 5–18 per minute average depth—women 8 5–15 per cent of estimated vital capacity men 8–14 5 per cent average ventilation—women 130–215 per cent of estimated vital capacity per minute men 115–190 per cent sighs less than 4 per 12 minutes swallows less than 1 per minute variation in rate 5 per minute or less variation in depth equal to or less than 10 per cent of estimated vital capacity variation in expiratory position 5 per cent of breaths or less miss base line by distance as great as 1/30 of estimated vital capacity inverted pattern absent rapid expiration absent Since only 27 per cent of the women and 17 per cent of the men showed a consistent pause at the end of expiration such a pause cannot be included as average behavior even though it is a sign of mental relaxation and is important in normal operation of respiratory muscles

[Normal and abnormal functional patterns are now widely recognized in the behavior of the cardiocirculatory and gastrointestinal systems and they occupy a large place in the rapidly developing field of psychosomatic medicine. The recognition of breathing patterns is rather new; the importance of identifying them is obvious in such conditions as asthma and other dysfunctions which may be alleviated by proper retraining of the patient in respiratory mechanics.—Ed.]

Value of Carbon Dioxide in Counteracting Effects of Low Oxygen was studied by F. A. Gibbs, E. L. Gibbs (Harvard Univ.) and L. F. Nims (Yale Univ.) in eight healthy young men. The study of arterial and internal jugular blood and of brain action by electro-encephalography before, during and after breathing of varying mixtures of nitrogen, oxygen and carbon dioxide revealed that normal brain function can be maintained despite percentages of oxygen in the inspired air as low as 2 per cent provided the carbon dioxide tension of the body is maintained. Addition of carbon dioxide to low oxygen mixtures permits maximal utilization of the available oxygen because of (1) increased pulmonary ventilation and consequent increased oxygenation of the arterial blood, (2) peripheral vasoconstriction and cerebral vasodilatation insuring to the brain a maximal share of the circulating blood, and (3) shift of the hemoglobin dissociation curve so that the blood unloads a greater proportion of its oxygen in the tissue. Improvement in the oxygen supply to the brain is only one aspect of the matter; maintenance of the carbon dioxide tension of the brain is equally important. Gross cortical dysfunction, manifested by high voltage slow activity in the electro-encephalogram and by mental confusion, occurs when the carbon dioxide tension of the brain falls as a result of breathing low oxygen mixtures even though the oxygen tension of the brain may be sufficient to maintain normal brain function. If the oxygen tension of the brain is lowered while the carbon dioxide tension of the brain is maintained, consciousness is lost without a preceding period of confusion and without the occurrence of high voltage slow waves in the

(6) A t M d 14 250 261 O t b 1943

electro encephalogram Breathing of low oxygen high carbon dioxide mixtures caused no unpleasant sensations or headache in the present series

These observations are directly applicable to submarine operation diving mining and all work in a closed space The increased respiration induced by high percentage of carbon dioxide in the inspired air is undoubtedly beneficial when the oxygen supply is reduced under such conditions but an inexperienced person might mistake the hyperpnea for a sign of distress and bring a carbon dioxide absorber into the space which might prove fatal to its occupants

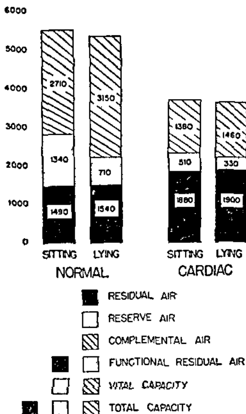
[In a recent review (Physiological Effects of CO on the Activity of the Central Nervous System in Man *Medicine* 22 205 221 September 1943) Mary A B Brazier of Boston discussed the complex mechanisms by which CO exerts its effects and emphasized that its value in high altitude flying must be judged not by any single functional effect but by the actual performance of the individual —Ed]

Lung Volume and Its Subdivisions in Upright and Recumbent Positions in Patients with Congestive Failure Pulmonary Factors in Genesis of Orthopnea McMichael and McGibbon showed that when normal subjects change from the sitting to the lying position characteristic findings are (1) little or no change in residual air (2) decrease in functional residual air due almost entirely to (3) decrease in reserve air (4) an increase in complemental air (5) a small decrease in vital capacity and (6) a small decrease in total capacity M D Altschule N Zamcheck and A Iglauer[7] (Harvard Univ) came to similar conclusions after studying the effects of changes in posture in 12 patients with chronic congestive failure of whom 9 had orthopnea of choice and 3 orthopnea of necessity (Fig 9)

The present study also revealed that no increase in degree of pulmonary congestion occurs on recumbency in orthopneic patients Changes in lung volume and its subdivisions which occurred in patients with mild and moderate orthopnea on change of position were similar to those which occur in normal subjects under comparable circumstances There was no further decrease in complemental

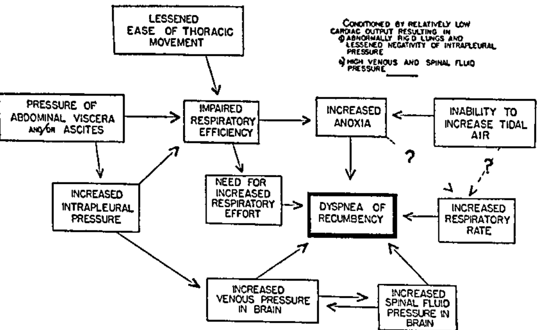
(7) J Clin Investigation 22 805 812 November 194

air on assuming the recumbent position or increase in the ratio of functional residual air to total capacity In 10 of 13 experiments there was a definite decrease in this ratio



F g 9—Eff t f po t hdı s d bı t t l g l m m l d

while in the other 3 the increases were insignificant Furthermore the changes observed on recumbency in decompensated patients without orthopnea were the same as in those with orthopnea The vital and total capacities de



F g 10 —Some f tors which i fl e oc enc f th pnea in p t nt ith h c e ng t f l

creased slightly owing to the fact that the complemental air failed to increase as much as the reserve air decreased

The decrease in reserve air and increase in complemental air on recumbency in normal subjects were shown by McMichael and McGibbon to be caused by a cephalad shift of the diaphragm due presumably to pressure of abdominal viscera Similar changes occurring in patients with congestive failure when lying down appear to be due to the same cause Application of an upper abdominal binder to three subjects while sitting caused approximately the same decrease in reserve air without change in the residual air as did assumption of the recumbent position Moreover application of the binder made the patients otherwise comfortable in this position dyspneic and increased respiratory minute volumes

A general conclusion is that orthopnea in congestive failure is due to the summation of the effects of complexly interrelated factors dependent chiefly on shift of the diaphragm Some of these factors are illustrated in Figure 10

Effects of Pleural Effusion on Respiration and Circulation in Man. Mark D Altschule and Norman Zamcheck (Harvard Univ) estimated the effects of pleural effusion in eight patients by comparison of measurements of the lung volume and respiratory and cardiovascular dynamics before and after thoracentesis

Significant changes were found after thoracentesis in all subdivisions of the lung volume except the residual and complemental airs the changes in residual air may be significant As the functional residual air rose somewhat immediately after thoracentesis it is concluded that pleural effusion causes atelectasis the collapsed lung re expanding some with removal of thoracic fluid Complete re expansion did not however occur for three to four weeks in the cases studied Accordingly overcoming of the atelectasis must be regarded as only of contributory importance in the immediate relief of dyspnea which may occur

(8) J Cl I tgt 23 3 5 331 My 1944

in thoracentesis Since removal of large amounts of fluid is followed by immediate increase in functional residual air of only some 100 cc elevation of the diaphragm must occur during thoracentesis In its depressed state the diaphragm permits only limited excursion and makes for inefficient respiration after resumption of its normal arch diaphragmatic respiratory excursion is greatly increased and respiration becomes more efficient Of the two components of the functional residual air the residual and reserve airs the former is only slightly affected by pleural fluid whereas the latter is markedly decreased Therefore the intrapleural pressure in the presence of fluid must be higher than normal Decreased negativity of the intrapleural pressure consequent to any cause impairs efficiency of respiration and also influences cardiovascular dynamics

The complemental air a measure of expansibility of the lungs is markedly diminished by pleural fluid The fluid *decreases pulmonary expansibility (1) by occupying space* within the thorax and (2) by causing atelectasis the atelectatic lung being less expansible than the normal Although the complemental air in these patients never decreased to the volume of the resting tidal air it was sometimes sufficiently small to prevent the normal increase in tidal air during exercise The decreased complemental air of pleural effusion therefore makes for anoxia during exertion and consequently contributes to dyspnea Decreased arterial oxygen saturation was found in only one patient but would probably occur in all during severe exertion Impaired expansibility of the lungs also favors dyspnea by requiring expenditure of more effort in attaining a given tidal air volume in this study the tidal air volume was decreased before removal of fluid The complemental air is little affected by thoracentesis attaining its normal volume only with complete re expansion of the atelectatic lung in the weeks after removal of the fluid

Study of the peripheral venous pressure showed that it is increased a manifestation of impaired venous return

consequent to changes in intrapleural pressure There were no changes in cardiac output or circulation time at least at rest as a result of pleural fluid

The authors conclude that pleural effusion impairs respiration and circulation in many ways thereby favoring occurrence of dyspnea and orthopnea these symptoms will be most severe in patients with extensive diffuse disease of the lungs in addition to the effusion

[The two preceding studies confirm by exact observation the cause of certain dysfunctions in these diseases The clinician therefore can plan his treatment with more intelligence —Ed]

Intrapulmonary Mixture of Gases Forms of Inadequate Ventilation in Normal and Emphysematous Lungs, Analyzed by Means of Breathing Pure Oxygen Robert C Darling Andre Cournand Dickinson W Richards Jr and Beatrice Domanski (Columbia Univ) state that if intrapulmonary mixing of air is perfect the concentration of nitrogen in the lungs at the end of any given number of breaths of pure oxygen can be calculated when (1) the effective tidal air volume (2) functional residual air volume (3) initial alveolar (intrapulmonary) nitrogen concentration and (4) rate of washing out the dissolved nitrogen in the body are known Conversely in actual experiments in which the subject breathes oxygen the degree of imperfection of mixture can be determined by the extent by which the nitrogen fails to reach the low value predicted by theoretical calculations

Values of pulmonary concentration of nitrogen after breathing oxygen were measured on 18 normal subjects and 5 *patients with severe pulmonary emphysema* For normal subjects the divergence between predicted and measured values was small in most instances but moderately great in a few Difficulties in accurate measurement of the upper pulmonary dead space make further clarification difficult but imperfect intrapulmonary mixture in some normal subjects is probable Four emphysematous patients showed markedly higher nitrogen concentrations in the lung than predicted indicating a marked degree of

(9) J Cl I t gation 23 55 67 J ry 1944

unequal lung mixture It was possible to demonstrate in actual clinical cases the distinction between inadequate ventilation of pulmonary spaces due to greatly increased residual air and that due to unequal mixture of tidal air through these spaces An estimation of the extent of under ventilation of pulmonary spaces in successive samples of alveolar air from normal and diseased subjects provided some evidence against the existence of any systematic alteration of function of discrete groups of alveoli

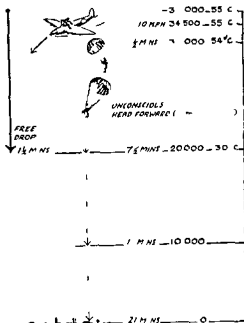
Some Aspects of Aviation Medicine Harold E Whittingham discusses altitude flying acceleration night vision and measures developed to prevent accidents and raise the general efficiency of flying personnel

To prevent anoxia or altitude sickness strict orders have been formulated regarding altitudes at which oxygen must be taken During the day oxygen must be used for all flights of over an hour at 10 000 ft and for all flights of 15 000 ft and above no matter how short At night oxygen must be taken during all flights above 4 000 ft and continued by gunner and pilot until the aircraft lands no matter what the height because oxygen aids greatly in night vision Oxygen containers developed include the mask a walk about oxygen bottle for moving about in the aircraft and a bail-out oxygen bottle fitting into the dinghy parachute pack Experiments have shown that a man could live 7½ minutes while unconscious when bailing out from 40 000 ft This is not adequate to insure safe descent as it takes at least 7½ minutes to reach 20,000 ft when a man bails out at 35 000 ft (Fig 11) Moreover the unconscious parachutist becomes limp and the head falling forward is liable to cause respiratory embarrassment The intense cold at these altitudes also reduces chance of survival A quicker descent could be made by doing a delayed drop from 35 000 ft to about 20 000 ft which would take 1½ minutes but by this time anoxia would be so great the man would fail to pull the rip cord Therefore the emergency bail out oxygen set was devel

(1) Glasgow M J 3 75 95 March 1944

oped which has added greatly to the confidence of airmen who are compelled to fly at the higher altitudes

Incidence of bends or decompression sickness at high altitudes can be reduced by careful selection of flying personnel and use of certain precautions Fit young men not



Fg 11—B l g t f m t ph

over 30 are less prone to bends than the more obese type in whom gas bubbles are more readily formed Physical and mental sluggishness and sleepiness caused by extreme cold are combated by carefully regulated addition of oxygen to the breathing Special measures prevent freezing of the oxygen mask and special clothing has been designed for flyers at high altitudes The blacking out which

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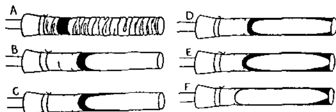
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(1) Glasgow M J 23 75 95 March 1944

EXPERIMENT 1—A short section of trachea from freshly killed hen was pinned horizontally to a small board and a mass of mucus collected from the respiratory tracts of several hens was introduced in the lower end occluding the lumen It moved by ciliary action from the lower to the upper end in a few minutes

EXPERIMENT 2—The mucus was recovered and again introduced into the lower end As soon as the mucus began to move the trachea behind it was stoppered and connected with



Fg 12—Chang in b p and p tion f ma f m cus d r g p su h g A p wh r pp w f d B m ad nced t t ll ng po t C m g d g by l t wh l m n m tat na y h ld by tm ph p D E nd F p og es d ce f m cu th n film to toppe ed nd of t hea wh t ll cts in a g M wh l l d g d pl gm grow p g ly tt er nd w k s ts ol me s r d d a d g b k tow d ta t g po t n th ca ng p b h nd it to g n D tt d l n show po t on when topp wa ntrod c d

a small water manometer Almost before the stopper could be secured negative pressur developed and reached —34 mm water in 18 minutes Eighteen repetitions gave similar results The farther the mucus advanced the more negative the pressure became and the more negative the pressure became the more slowly the mass progressed Finally it came to a complete stop greatest negative pressure being —40 mm water

EXPERIMENT 3—One experiment was continued 50 minutes Pressure in the manometer was maintained at the maximum for 8–10 minutes then began to decrease It finally returned to —6 mm from a maximum of —14 mm Meanwhile the mucus began to appear at the unstoppered cut end of the trachea where it formed a thick ring The stopper was removed since apparently all mucus had been transported and since the remaining pressure of —6 mm appeared to be the effect of capillarity The water in the manometer promptly equalized Inspection of the trachea showed a thin transparent diaphragm of mucus still intact this apparently had maintained the —6 mm pressure The cilia obviously had con

occurs while making tight turns or pulling out from a steep dive at high speeds caused by sudden drainage of blood from head to feet can be prevented somewhat by bending over during such maneuvers thus reducing height of the column from brain to heart Selection of suitable personnel also helps in this problem Special selection of personnel training optical aids and other measures neces sarily secret have been used in coping with the problem of night vision

[Among various other studies of the effects of altitude are sev eral of particular interest to the clinician J H Tillisch *et al* Study of the Effects of Airplane Transportation of 200 Patients *Journal of Aviation Medicine* 14 162 172 August 1943 G S Todd Effect of Altitude on Cases of Pneumothorax *Lancet* 2 597 600 Nov 13 1943 E W Peterson B S Kent H R Ripley and D R Murphy Investigation of Pneumothorax and Respira tory Function at Altitude *Canadian Medical Association Journal* 50 520 523 June 1944

Among the conclusions are these A patient with a small pneumothorax (20 per cent collapse) did not lose any significant respiratory reserve up to altitudes of 20 000 ft but one with a 50 per cent collapse had marked symptoms from such loss at 15 000 ft Oxygen should be given from ground level where possible A patient with a chest wound and resulting pneumothorax had better not go above 4 000 ft unless pleural pressure is adjusted *previously In a case of tension pneumothorax due to lacerated* lung an intercostal needle or catheter should be put in place prior to the ascent to permit adjustment of pressures Patients who have severe cardiac or pulmonary di ea e or who have undergone recent abdominal operation shoul l fly nly when absolutely nece sary — Ed]

Production of Negative Pressure in Respiratory Tract by Ciliary Action and Its Relation to Postoperative Atelectasis A C Hilding* (Duluth Minn) does not agree with the opinion that atelectasis is caused by bron chial obstruction by firmly fixed masses of mucinous secre tion which accumulates because of reduced respiratory force that air trapped beyond the obstruction is absorbed by the blood stream and that the condition can be pre vented by deep breathing and coughing Believing that this concept does not give the ciliary mechanism due con sideration he conducted experiments to shed further light on development of atelectasis

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Pressure was maintained near maximum for almost an hour showing that the negative pressure developed was not due to absorption The experiment was repeated four times Maximum pressure was +55 mm

Hilding s conception of the formation of atelectasis based on these experiments is presented in Figure 14 The steps shown would be repeated many times since one mucinous piston advancing up the bronchus would not produce collapse there would have to be a succession each carrying

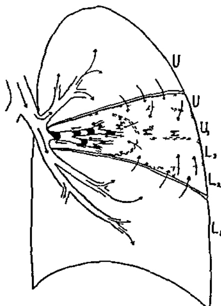


Fig 14

a volume of air somewhat on the principle of a mercury vacuum pump The pistons would continue to advance and be carried away as long as any considerable amount of air remained in the lobe They would not stand still until pressure in the lobe had fallen to such an extent that the effective power of the cilia had been overcome this would

tinued to exert traction with the result that the mucus was dragged away at the periphery and carried progressively to the unstoppered end of the trachea in a thin film (Fig 12) The volume of the piston was thus reduced thereby reducing thickness and strength As it became thinner it could no longer maintain maximal pressure and sagged back in the middle thus reducing negative pressure This continued until all mucus had collected in a thick ring and negative pressure had practically disappeared

EXPERIMENT 4—There remained the possibility that the air

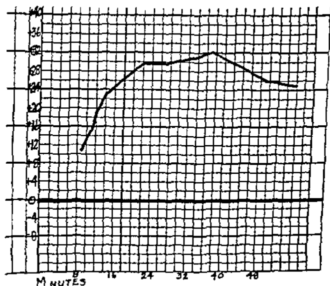


Fig 13—P t p n se t n of trachea f m fr hl k ll d hen Occlud g m s of m cu wa nt od ced to lowe nd nd upper or lary g al end w st pp ed a d con ected w th th manom t r Th shows that neg t ve p f d pe m t was n t e lt of bso pt o f r by the t ue

in the excised trachea used in the previous experiments might have been absorbed by the tracheal tissue thus producing reduced pressure Therefore the section of trachea was reversed i e the upper or laryngeal end was stoppered and connected with a manomet r When the mucus was introduced at the lower end and was carried up by ciliary action positive instead of negative pressure promptly developed (Fig 13)

Stevens (Queen s Univ Kingston Ont) Factors re sponsible for excretion of R T F (respiratory tract fluid) from the lungs and through the trachea in urethanized animals with tracheal cannula are (1) ciliary drainage (2) movement due to action of voluntary muscles of respiration and (3) contractions of the bronchial muscles of Reisseissen Cough and reabsorption also play a part but did not in the present experiments If the drainage mechanisms are ineffective or incapable of excreting R T F as fast as it is produced an increased output of R.T F should result from postural pulmonary drainage

In the normal urethanized animal postural pulmonary drainage does not increase the output of R T F hence the mechanisms are sufficient and effective When the ciliated mucosal lining of the trachea of rabbits and cats is dam aged by inhalation of ammonia or live steam output of R T F is doubled or tripled by postural drainage but drainage is incomplete and about the normal rate when the animals do not have postural drainage Hence mecha nisms 2 and 3 may be assumed to be geared to handle not more than the normal load of R T F When the output of R T F in rabbits and cats is doubled or tripled by giving cholinergic drugs or by faradic stimulation of the cervical vagus nerve the output is not augmented by postural pul monary drainage the ciliated mucosa is not damaged and hence it may be concluded that the ciliary drainage mecha nism is geared to handle loads of R T F greater than normal In sick cats and dogs with normal tracheobron chial mucosa but with congestion of the pulmonary alveoli postural drainage did not augment outputs of R T F which on the average were 8–15 times normal and in individual animals as high as 50–100 times normal Hence the reserve capacity of the cilia to excrete R T F must be great Cough is not likely to be useful and productive therefore except if there is extensive damage to the tracheobronchial mucosa or when the cilia are bathed in a markedly nonphysiologic medium such as pus Postural

(3) Am J Phy 1 140 467 473 J y 1944

not occur until the air in the lobe was exhausted and the lobe had collapsed

Medically the steps in production of postoperative atelectasis follow the diagram in Figure 14 (1) Excess of secretion is formed in the lobe as result of anesthesia reflex stimulation or a combination of these and other causes (2) Occluding masses or pistons of mucus form across the lumen owing to force of inspired air changes of diameter of air passages during respiration viscosity and volume of secretion size of air passages reduced respiration due to pain etc (3) The pistons move up the cylindric passage by ciliary action each carrying a quantity of air (4) When air pressure in the lobe begins to fall the lobe shrinks by its own elasticity and by pressure *from surrounding lobes* (M_1 M M_3) (5) *Surrounding* lobes by force of inspired air move into space relinquished by the affected lobe (U_1 U_3 L_1-L_3) Changes in position of the lobes and their shrinkage and distention are facilitated by the sliding motion of the lungs during respiration The advancing mucous pistons rupture serially as they reach tubes of greater diameter and meet more forceful changes of air pressure releasing air bubbles and continuing as mural films (6) Pressure in the affected lobe becomes so negative that the mucous masses in the air passages come to a standstill against atmospheric pressure These are the so called fixed mucous plugs but although static they are not actually fixed

[Hilding's work helps materially to clarify our understanding of bronchial ciliary mechanics and their great importance The mucous plug theory of bronchial obstruction is widely and glibly used but seldom demonstrated certainly its dynamic action has not been clear Be this as it may there are still many misconceptions of the alveolar changes distal to the affected bronchi *The diagnosis* of atelectasis usually is an assumption not supported by adequate evidence As a rule there is little or no diminution in the volume of the affected pulmonary segment or lobe and its increased density is probably due most often to accumulated serum secretions and inflammatory exudate —Ed]

Effect of Damage to Tracheal Mucosa on Drainage of Respiratory Tract Fluid was investigated in rabbits cats and dogs by *Eldon M Boyd W F Perry* and Mary E T

many drugs commonly used in the nose and throat and is especially inhibited by an alkaline environment the optimal pH for best functioning of the ciliary organ is between 5 5 and 6 5

Persons with chronic bronchial infection and with bronchiectasis are liable to recurring attack of pneumonia It is easy to understand how destruction of the ciliated epithelium may be responsible for failures in removing inhaled bacteria and how spaces with accumulated fluids may furnish these bacteria with an ideal medium for multiplication

The commonest condition predisposing to pneumonia is that produced by the common cold Information so far obtained does not deny the possibility that the cold virus in attacking the cells of the ciliated epithelium may temporarily block the protective function of that organ and thus make bacterial invasion possible In whooping cough also a well known precursor of pneumonia the importance of the ciliary organ is emphasized when it is found that bacilli have worked their way through the layer of mucus and are situated among the bases of the cilia Once in the airways and unencumbered by the ciliary defenses they are free to grow and mobilize The resulting reaction is an inflammatory exudation from the denuded or paralyzed membrane cells and fluid appearing from the capillaries of the underlying stroma Fluid may also be aspirated from above Coughing reflexes strive to hoist up the gross material as sputum but between coughs it tends to flow back by gravity As the area involved grows more exudate appears When the alveoli at the terminal ends of the bronchial twigs are reached they fill with exudate producing solidification and relatively large amounts of intrabronchial fluid are then present The part which may be played by chronic passive congestion of the lungs under these circumstances is obvious

Robertson s work on the importance of these fluids in extension of pneumonia has widened the insight of inception and extension of lobar pneumonia considerably The

pulmonary drainage is likely to be effective only under the same conditions

[The importance of finely adjusted physiologic mechanisms for the drainage of the bronchi and lungs cannot be overestimated. Failure of one or more of them is one of the most obvious predisposing causes of pneumonia. This is properly emphasized in the following article by O Hara—Ed.]

THE PNEUMONIAS

Mechanisms Predisposing to Pneumonia Dwight O Hara (Tufts College) states that the ciliary membranes of the respiratory tract are chief among the mechanisms of resistance of the infected or prospective host. Roentgenograms have shown involvement of a definite area in the reaction of the pulmonary system to any sort of inhalational injury. This area is most concentrated in the central regions occupied by the trachea and larger bronchi and continues outward in diminishing degree until it disappears as it approaches and reaches the periphery. It is often visualized by the pulmonary silhouette of the patient with pneumoconiosis due to inhalation of silica, iron or asbestos. Anatomically this in turn corresponds to the distribution of the ciliated mucous membrane lining the respiratory tract. The membrane is most highly developed in the trachea and larger bronchi, where it is a deep columnar epithelium rich in goblet cells and deeper gland structures. As the smaller bronchi are reached the epithelium becomes thinner, the columnar cells at first become shorter and then are replaced by cuboidal cells, which in turn become patchy in distribution and finally yield to the stratified epithelial cells which line the bronchioles. As the columnar cells become shorter and disappear the effective ciliary apparatus becomes sparser and less highly developed.

The continual functioning of this ciliary organ should be remembered when prescriptions are made for colds or other minor respiratory illness because it is sensitive to

(4) Bull New England M Cent 6 97 101 June 1944

suffer from some degree of chronic tracheobronchitis which under normal conditions may be nearly asymptomatic The existence of this condition is overlooked After laparotomy basal hypoventilation and restriction of efficient coughing bring about stagnation of bronchial secretion which is often already excessive in smokers The secretion accumulates and becomes infected and purulent and true bronchitis develops Bronchial block and a major complication may follow alternatively the sputum may be coughed out as vital capacity and muscular power return and pain diminishes and before a more serious complication develops When there is little or no postoperative interference with vital capacity or coughing e g after most nonabdominal operations this succession of events is probably avoided at its outset Thus in 350 major non abdominal operations only 1 case of pulmonary complication was observed Total complication rate was about three times greater in males which is in keeping with general opinion Further analysis shows however that the morbidity rate was about the same for the two sexes It may be assumed that in the usual statistical studies the preponderance of complications in males reflects the far larger proportion of heavy smokers among male patients which group in either sex carries the greatest morbidity rate In this series cyclopropane anesthesia was used since this is relatively nonirritating to the respiratory tract the complication rate for the male smokers was probably reduced thus accounting for the more nearly equal sex incidence

When abdominal operations are contemplated it is advisable for smokers to stop or reduce their smoking as a precaution against pulmonary complications

[It is a common experience for patients with chronic cough and mucoid expectoration sometimes with asthmatoid bronchitis to find relief merely by stopping smoking The excessive wetness of the mucous membranes caused by heavy smoking predisposes to infection and is probably the chief factor in the postoperative complications described by Morton —Ed]

Pneumococcic Capsular Swelling Reaction, Studied with Aid of the Electron Microscope is described by

practical result of his work deals with care of the lobar pneumonia patient who seeks aid only after the disease has been present for several days Such a patient presents wet lung processes and sulfonamide therapy is usually of no avail Involvement spreads from lobe to lobe while the patient becomes toxic dyspneic and cyanotic and has abundant and often bloody sputum tachycardia and abdominal distention If the involvement is primarily of one side the patient should be placed on that side with head and thorax somewhat raised Unless this position is specifically ordered and watchfully guarded nurses may roll the patient back and forth thus inviting extensions to the other side

Experimental investigation of the time honored association between alcoholism and pneumonia showed that alcohol produces cessation of ciliary movement thus preventing this organ from fulfilling its protective functions

Tobacco Smoking and Pulmonary Complications after Operation H J V Morton[5] reports a statistical investigation of whether the heavy tobacco smoking habit carries with it an added risk of postoperative pulmonary complications based on study of the incidence of bronchitis atelectasis and bronchopneumonia after abdominal operations and gas oxygen ether anesthesia in 1 257 adults

The use of omnopon scopolamine a mild respiratory depressant for premedication was associated with a slight but not significant increase in pulmonary complications when compared with atropine alone which has no depressant effect The combined figures for all types of abdominal operations show that the morbidity rate for persons smoking more than 10 cigarets or ½ oz tobacco daily is about six times that for nonsmokers Smokers are more likely to have complications associated with serious constitutional disturbance

The production of mucopurulent sputum 12–18 hours after operation in absence of a previously infected bronchial mucous membrane may indicate that many smokers

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suffer from some degree of chronic tracheobronchitis which under normal conditions may be nearly asymptomatic The existence of this condition is overlooked After laparotomy basal hypoventilation and restriction of efficient coughing bring about stagnation of bronchial secretion which is often already excessive in smokers The secretion accumulates and becomes infected and purulent and true bronchitis develops Bronchial block and a major complication may follow alternatively the sputum may be coughed out as vital capacity and muscular power return and pain diminishes and before a more serious complication develops When there is little or no postoperative interference with vital capacity or coughing e g after most nonabdominal operations this succession of events is probably avoided at its outset Thus in 350 major non abdominal operations only 1 case of pulmonary complication was observed Total complication rate was about three times greater in males which is in keeping with general opinion Further analysis shows however that the morbidity rate was about the same for the two sexes It may be assumed that in the usual statistical studies the preponderance of complications in males reflects the far larger proportion of heavy smokers among male patients which group in either sex carries the greatest morbidity rate In this series cyclopropane anesthesia was used since this is relatively nonirritating to the respiratory tract the complication rate for the male smokers was probably reduced thus accounting for the more nearly equal sex incidence

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Pneumococcic Capsular Swelling Reaction, Studied with Aid of the Electron Microscope is described by

Stuart Mudd Ferdinand Heinmets and Thomas F Anderson[6] (Univ of Pennsylvania) The pneumococci used were capsulated type I and III strains grown on fresh 5 per cent horse blood agar plates The electron micrographs revealed that the pneumococcic capsule is a gel of

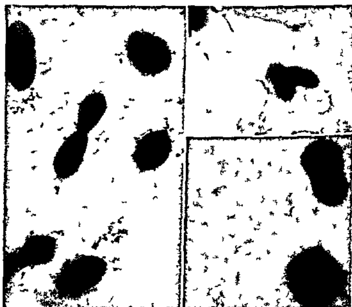


Fig 15 (left) —Caps l ted cells of pneumococcu type III Not exposed to s um
Fig 16 (t p right) —Pn mococcus type III aft r 30 second exp sure to 1 10 d l t n of het ol gou (typ I) abb t ant serum.
Fig 17 (bott m right) —Pneumo occu type III fter two n n tes exposur t 1 10 d l t n of type III r bb t tiserum.

low density outside of and closely applied to the bacterial cell wall Interaction with homologous immune rabbit serum greatly increases the thickness and density of this capsular gel the increase in thickness of the specifically swollen pneumococcic capsule may exceed by 25 fold the thickness of the surface deposit caused by rabbit immune serum on the cell walls and flagella of homologous non

(6) J E p M d 78 3 7 33 No mbe 1943

capsulated bacteria Conclusions drawn from these and earlier data are that homologous immune serum permeates the pneumococcic capsular gel the specific antibody combines with the capsular polysaccharide and nonspecific serum components are secondarily adsorbed to or combined with the specific antigen antibody complex The relatively low antibacterial titers characteristic of pneumococcic antiserums can be explained in part by the permeation of the capsule by antiserum and in part by the high combining capacity of pneumococcic carbohydrate for antibody

Figure 15 shows pairs and individual cells of pneumococcus type III The bacterial protoplasm in this preparation fills the cell walls completely so that the cell wall is not visible as a separate structure the capsule surrounds the cell wall as a sort of aureole In Figure 16 although the considerable concentration of protein has left an obvious deposit on the collodion mount the capsules of the pneumococci are little affected by the heterologous serum In Figure 17 permeation of the capsule by serum with increase in size and density is obvious

Studies on 2 Sulfanilamido-4-Methyl Pyrimidine (Sulfamerazine, Sulfamethyldiazine) in Man Treatment of Pneumococcic Pneumonia Harrison F Flippin William I Gefter Albert H Domm and Jefferson H Clark (Philadelphia Gen l Hosp) gave 80 patients sulfamerazine and 80 sulfadiazine With sulfamerazine two dosage schedules were used initial 3 Gm dose by mouth followed by 1 Gm every six hours to the first 23 patients and the same initial dose with 1 Gm every eight hours to 57 patients With sulfadiazine initial dosage was the same followed by 1 Gm every six hours Average total dosage for patients successfully treated with sulfamerazine was 24 4 Gm (4 Gm daily for 5 6 days) or 22 7 Gm (3 Gm daily for 6 5 days) and for sulfadiazine 30 8 Gm (4 Gm daily for 7 days) For rapid elevation of blood level the initial 3 Gm dose of either drug was given intravenously as 5 per cent

(7) Am J M S 206 216 1 A g t 1943

sodium salt solution Serum was given when chemotherapy failed to bring favorable response in 37–48 hours

Of the sulfamerazine group six died (7 5 per cent) while eight died in the sulfadiazine group (10 per cent) Mortality rate with bacteremia in the sulfamerazine group was 33 per cent in the sulfadiazine group 18 2 per cent A critical drop in temperature occurred in 24 hours in 51 4 per cent of the sulfamerazine group and 30 6 per cent of the sulfadiazine group Within 48 hours 77 per cent of *the sulfamerazine group and 66 7 per cent of the sulfa*diazine group showed a critical drop in temperature Temperature returned to normal in 24 hours in 17 5 per cent of the sulfamerazine group and 15 3 per cent of the sulfadiazine group Corresponding figures for 72 hours were 72 9 and 59 8 per cent respectively The more rapid fall in temperature in the sulfamerazine group may be related to the more rapid rise and higher concentrations of the drug in blood Average concentration of free sulfamerazine in plasma was 12 7 and 10 9 mg per cent of free sulfadiazine 7 9 mg per cent

Incidence of complications was low in both groups One patient given sulfamerazine developed endocarditis and one meningitis two patients given *sulfadiazine developed en*docarditis and three empyema Incidence of toxic reactions was likewise low and comparable for the two groups *Vomiting occurred in two patients of each group* hematuria in three patients receiving sulfamerazine and four given sulfadiazine and crystalluria in about 15 per cent of each group No instance of blood dyscrasia or skin rash was noted Drug fever occurred in three cases

Treatment of Pneumococcic Pneumonia with Sulfapyrazine Results in 105 cases are reported by J M Ruegsegger Norris L Brookens Morton Hamburger Jr and Eda S Grupen[8] (Univ of Cincinnati)

During the early part of the study all patients received an initial dose of 2–4 Gm followed by 1 Gm every four hours all given orally Later the initial dose of 4 Gm was

(8) Am J M Sc 06 3 3 3 7 Septemb 1943

given intravenously as a 5 per cent solution of the sodium salt and the maintenance dose was as before Because of a few instances of renal irritation maintenance dose was changed to 1 Gm every six hours and no patient showed renal toxicity The drug was administered routinely until rectal temperature remained below 99 F for 48 hours Average total dose was 30 4 Gm Types I II III V VII and VIII accounted for over 70 per cent of the total Twenty three per cent of the patients had bacteremia when chemotherapy was begun All but four patients recovered The fatalities occurred in patients with bacteremia they were with one exception over 50 and had signs of degenerative disease

Improvement in clinical condition was usually apparent in 12–24 hours and was apparently independent of the temperature A critical fall of temperature occurred in 45 per cent of nonbacteremic patients and in 16 per cent of the recovered bacteremic patients The only important toxic effect of the drug was on the kidney Evidence of transient renal damage as evidenced by elevation of the blood urea nitrogen occurred in 9 per cent of the patients given 1 Gm every four hours No patient developed clinical signs of uremia and in every instance the blood urea nitrogen returned to normal after the drug was discontinued and proper fluid intake established Of 44 patients given 1 Gm every six hours a few blood cells were discovered microscopically in six cases The other toxic effects commonly produced by sulfonamides were rare One morbilliform rash one instance of nausea and vomiting and two of fever may have been due to the drug

[Another preparation which has been investigated is sulfamezathine (also called sulfamethazine) which is the 4 6-dimethyl pyrimidine compound of sulfanilamide Reports by Morgan and Wylie Smith (*Lancet* 2 731 733 Dec 11 1943) by Melton (*Lancet* 1 277 278 Feb 26 1944) and by Loughlin Bennett and Flanagan (*Journal of Laboratory and Clinical Medicine* 29 568 573 June 1944) indicate that it is an effective drug with relatively low toxicity especially on the kidney Renal irritation may be avoided or minimized when giving sulfonamides by adequate fluid intake (3000–4 000 ml in an adult) and by the use of alkali sufficient to maintain an alkaline reaction of the urine according to

the recommendation of the Pneumonia Technical Advisory Committee to the Department of Health of the City of New York (*Bull tin of the New York Academy of Medicine* 20 190 193 March 1944) Six Gm of sodium bicarbonate as an initial dose followed by 2 5 Gm every four hours is suggested except when nephritis or other contraindicating disease is present

It is widely agreed that sulfonamides should not be administered for unnecessarily long periods or on trivial indications such as mild upper respiratory infections One result may be the development of drug resistance by the organisms which the patient harbors

Various allergic reactions to the sulfonamides have been described among these Pinkerton reports pulmonary lesions resembling those of virus pneumonia See also Rich and Gregory this YEAR BOOK p 179—Ed]

***Treatment of Lobar Pneumonia and Pneumococcic* Empyema with Penicillin** William S Tillett Margaret J Cambier and James E McCormack (New York Univ) report on 46 cases Patients selected for penicillin therapy had on admission lobar consolidation and a degree of severity indicating the probable pneumococcic etiology of the infection In only three cases was the specific etiology undetermined In 32 infecting pneumococci were types I to VIII in 13 of these there was bacteremia

Penicillin was supplied as dry powder in sealed ampules and kept in the refrigerator Solutions for injection when prepared in advance were also refrigerated but were not retained longer than a day or two Solutions of penicillin were given by repeated injections either intravenously or intramuscularly For intravenous injection the powder was dissolved in physiologic salt solution or sterile water in the ratio of 1 000 units to 1–1 5 cc solution For intramuscular injection ratio was 1 000 units to 0 3 cc solution so that the usual individual dose of 10 000 units was contained in 3 cc For cases of relatively moderate severity the intramuscular route is efficacious while for more seriously ill patients or those with bacteremia the intravenous route appears preferable In cases of moderate severity 10 000 units of penicillin given intramuscularly every three hours for four doses on each of three and possibly four successive days appears satisfactory while for seriously ill patients 25 000 units intravenously every three hours for

(9) B ll New York A d Med 0 14 178 M h

the first two doses on the first day followed by 10 000 units intramuscularly at three hour intervals for the second two doses on the first day is satisfactory and for treatment the second third and fourth day four doses of 10 000 units every three hours for each day

Of the 46 patients 3 died and 39 recovered The response was not clearly defined in four patients one of whom probably had primary atypical pneumonia and the other three unrelated underlying pulmonary diseases which prolonged their illness beyond the usual course of pneumonic resolution In the remaining patients the rapidity of drop in temperature was striking occurring usually within the first 12–20 hours Alleviation of symptoms was marked respirations slowed to normal rates coincident with improvement although cough persisted for several days There were no untoward depressive physiologic reactions referable to the rapid critical change in the condition Resolution of the consolidated areas seemed to progress more rapidly than with sulfonamide therapy The leukocyte count was unaffected by penicillin and returned to normal within four to six days The only toxic reaction was an occasional pyrogenic one about one hour after injection and lasting about two hours

In 14 patients with bacteremia the second blood culture was sterile in each following penicillin therapy Total dosage during the first 24 hours in this group ranged from 30 000 to 105 000 units intravenously The findings in the bacteremic cases as well as in those of pneumonia only suggest that maintenance of a definite level of penicillin continuously may not be necessary

Comparative studies of the values of penicillin and sulfadiazine therapy in pneumonia indicate that penicillin is particularly serviceable when pre existing sensitivity to the sulfonamides prevents their use or when sulfonamide toxicity develops during treatment before the infection has been completely overcome Furthermore penicillin was highly effective against sulfonamide fast pneumococci as shown experimentally

Eight patients with pneumococcic empyema were treated by intrapleural injections of penicillin In seven the infection was eliminated by local therapy without surgical drainage Six of them recovered completely with only a restricted area of pleural thickening remaining as permanent alteration In one patient with pyopneumothorax on admission the pyothorax cleared up satisfactorily but the pneumothorax arising from a bronchopleural fistula present before treatment persisted In another patient who was insufficiently treated with penicillin at the beginning relapse occurred and surgical drainage was instituted After discharge the patients were re examined after one week in one case and after four to six months in the others With the exception of the patient with pneumothorax all had remained free of symptoms Solutions of penicillin used were mostly made up in concentration of 1 000 units of *penicillin in 1–1 5 cc physiologic salt solution* The quantity injected was never in excess of the amount of exudate removed Experience in these cases suggests that 30 000–40 000 units is an adequate dose and three separate injections may in most cases be sufficient when clinical improvement appears to be progressive and the exudate remains sterile At the time of bedside aspiration the cavity should be irrigated with a few hundred cubic centimeters of physiologic salt solution before introducing the penicillin this may be repeated if necessary at intervals of several days after treatment is stopped to hasten removal of degenerated sterile exudate and to minimize reaccumulation of effusion

Comparative Activity of Sulfonamides against Klebsiella Pneumoniae (Friedlander's Bacillus) Clara L Sesler and L H Schmidt (Cincinnati) tested the activity of sulfapyrazine sulfadiazine sulfathiazole sulfapyridine and sulfanilamide against infections with four strains of Friedlander s bacillus in mice Two groups of experiments were carried out

1 In tests of activity of sulfonamides administered in

(1) J Ph rma ! & E pe Th p 79 117 1 6 October 1943

equal doses all mice given sulfadiazine and 77 per cent of those given sulfapyrazine recovered whereas only 3 per cent of those given sulfathiazole and sulfapyridine and none of those receiving sulfanilamide recovered The effectiveness of any drug varied with the strain of the bacillus Sulfadiazine cured only 34 per cent of mice infected with strain GH but 100 per cent of those infected with strain S or E Sulfapyridine hardly affected infections with strains GH H and E but cured 80 per cent of mice infected with strain S Similar differences were noted among the other drugs

2 In tests of activity of sulfonamides given in doses maintaining similar concentrations in the blood sulfapyrazine and sulfadiazine had much greater activity than sulfapyridine sulfathiazole or sulfanilamide The action of sulfapyrazine and sulfadiazine was identical with three strains and differed only with strain H The activity of sulfadiazine at a dosage of 0 5 mg was similar to that at 2 5 mg except with strain H when the effectiveness was considerably less with the smaller dose Of the three less active drugs only sulfathiazole showed a rise in activity with increase in dosage These experiments re emphasize the difference in effectiveness of sulfonamides against different strains of Friedlander s bacillus With strain H only sulfapyrazine had a curative effect and then in only 6 of 30 mice However all five drugs even sulfanilamide were effective against strain S

The order of activity of the different drugs in vitro was influenced by composition of the medium In beef heart broth sulfathiazole was the most effective sulfapyrazine sulfadiazine and sulfapyridine about equal and sulfanilamide the least active In synthetic medium sulfathiazole sulfadiazine and sulfapyrazine were about equal sulfapyridine less active and sulfanilamide the least active There was no correlation in the order of activity in vitro with that in vivo except for sulfanilamide which was least active in both Sensitivity of the various strains varied with the test medium strain E being more sensitive than strain

H in beef heart and strain H being the most sensitive of the strains tested when grown in synthetic medium

The in vivo experiments suggest that sulfadiazine or *sulfapyrazine* are the drugs of choice in treatment of Friedlander s bacillus infections

Studies on Etiology of Primary Atypical Pneumonia Monroe D Eaton Gordon Meiklejohn and William van Herick (Berkeley Calif) describe experiments during which a filtrable virus from certain cases of primary atypical pneumonia was transmitted to chick embryos by inoculation of the amnion with suspensions of bacteriologically sterile lung tissue or filtered sputum three strains were adapted by passage On intranasal inoculation of cotton rats and hamsters suspensions of the infected chick embryo tissues produced pulmonary lesions similar to those seen after instillation of infective human material and pathologically resembling those seen in virus pneumonia The agent propagated in chick embryos was specifically neutralizable by serum from patients recovered from primary atypical pneumonia and was not neutralized by acute phase specimens Passages of the virus in cotton rats and hamsters gave confusing results because of contamination with latent respiratory agents already present in the animals

The proportion of all cases of primary atypical pneumonia caused by the described virus is not known This can probably be found most effectively by neutralization tests in a large series of cases Results of sputum inoculation of cotton rats suggested that when fresh material is taken soon after onset of the disease almost half the specimens contain the infectious agent Evidence also indicates an association of the *virus transmissible to cotton* rats with that in cases in which cold agglutinins are found in the serum It is probable that certain respiratory diseases without pneumonia are caused by the same virus

[The Commission on Acute Respiratory Diseases Fort Bragg N C (*American Journal of Public Health* 34 335 346 April 1944) found evidence in epidemiologic studies to support the suspicion that the causative agent of common upper respiratory disease and atypical pneumonia is one and the same —Ed]

( ) J Exp Med 79 649 668 June 1944

Atypical Pneumonia Caused by Psittacosis-Like Viruses Gordon Meiklejohn M Dorothy Beck and Monroe D Eaton (Univ of California) report on 10 cases in which etiology was determined by isolation of the virus and by serologic tests and on 2 related cases which apparently were sources of infection The strains of virus isolated fall into two types one of which probably originated in pigeons designated pigeon ornithosis virus and the other of unknown origin but probably identical with strains isolated in 1940 designated S F

Four patients with naturally occurring infections with pigeon ornithosis virus gave history of contact with pigeons in one case very transient They presented the picture of severe systemic infection with bronchopneumonia of variable extent Two died one after the infection had apparently subsided and presumably owing to age and cardiovascular status and the other of fulminating infection and rapidly extending bronchopneumonia The virus of pigeon ornithosis was isolated from the sputums of all four patients and in two instances a similar virus was isolated from pigeons in flocks presumably responsible for infection of the patients

Among six naturally occurring infections presumably due to the strain S F (cases not related to contact with birds) four occurred in nurses attending the two original patients pointing to high person to person communicability Five cases were fatal The two laboratory infections occurred during routine investigation of the virus and re emphasize the danger of work with psittacosis agents particularly when inoculations are done by the intranasal route

It is impossible to differentiate between pneumonias due to psittacosis like viruses and typical primary atypical pneumonia not caused by the e agents However most primary atypical pneumonias are mild with comparatively few moderately severe and even fewer extremely severe or fatal with the psittacosis like viruses most

(3) J Cl I t g t 23 167 1 5 M b 1944

infections have been moderately or extremely severe and case fatality has been high Symptoms more common in the psittacosis like group include frequent chills usually at onset gastro intestinal symptoms desperate illness even though the area of pulmonary infiltration is not great and respiratory distress slight marked disturbance of cerebral function and useful mostly in retrospect greater duration and height of fever

The complement fixation test has been used in diagnosis of psittacosis like infections in most recent reports Among its limitations are the group specific character of the re action thereby giving little information as to type of *virus or source of infection* and the fact that other diseases such as lymphogranuloma venereum may pro duce high antibody titers with psittacosis antigen Demon stration of complement fixing antibodies in a single specimen of serum from a patient with atypical pneumonia does not justify diagnosis of psittacosis or a related dis ease although absence of antibodies during convalescence may exclude it Also certain normal human beings may have developed antibodies as result of contact with the agents Pneumonia of any kind may occur in a person with pre existing psittacosis antibodies and demonstra tion of virus or antibodies in birds with which the patient is associated may be coincidental Isolation of virus from the patient and demonstration if possible of a definite antibody response associated with the illness constitute the only satisfactory positive evidence of specific infection

Clinical Aspects of Primary Atypical Pneumonia A study based on 1 862 cases seen at the Station Hos pital Jefferson Barracks Mo from June 1942 to August 1943 is presented by Arie C van Ravenswaay George C Erickson Edward P Reh Joseph M Siekierski Ruben R Pottash and Bernard Gumbiner Mortality rate was 0 26 Incidence of infections usually reached its peak during the initial period after arrival at the barracks and dropped considerably thereafter probably

(4) J A M A 124 1 6 Ja 1 1944

because of development of specific immunity Frequency of colds in new arrivals may explain this immunity The theory of a common causation of primary atypical pneumonia and associated cases of upper respiratory tract infection is further supported by apparent ab ence of cross infection in wards for upper respiratory disease after exposure to patients with primary atypical pneu monia Incubation period was estimated to be between 7 and 15 days

Careful study of symptoms and physical signs in 297 consecutive cases of primary atypical pneumonia (Tables 1 and 2) demonstrates a much greater virulence of the

TABLE 1—ATYPICAL PNEUMONIA INCIDENCE OF SYMPTOMS IN 297 CASES

	Sympt m	Occurrence %
Onset	Gradual	67.2
	Acut	3? 8
Constitutional symptoms	Fe erishness	85 5
	Malaise	70 4
	Chilline	68 0
	Headache	48 0
	Rigor	11.5
Symptoms referable to respiratory tract	Cough	86 2
	Sputum	
	Nonbloody	49 0
	Blood streaked	23 9
	Bloody	2 4
	P une ju	0 4
	Coryza	49 0
	Sore throat	47 0
	Thora ic pain	69 5
	Subst rnal	20 4
	Pleural on mot on	47 7
	Thoracic on re t	11.2

TABLE 2—ATYPICAL PNEUMONIA INCIDENCE OF PHYSICAL SIGNS IN 297 CASES

S gns	Occur ce
Fever	97 6
Rales	56.2
Dulness	28 0
Dyspnea	21 7
Diminished breath sounds	19 0
Consolidat on	9 8
Frict on rub	7.7
Fluid	6 1
Cyanosis	3 6
Meningeal s gn	0 4

disease in this series than in those previously reported indicated by the higher maximal temperatures and greater incidence of chest pain bloody sputum and complications Approximately two thirds had gradual onset with upper respiratory infection for days or weeks followed by malaise fever cough and chest pain One third had acute onset Severe headache was common and at times associated with meningeal signs The most helpful physical sign was presence of rales (56 2 per cent) which were

TABLE 3—COMPARISON OF RESULTS OF TREATMENT BY PROLONGED BED REST AND OF CONVENTIONAL TREATMENT

	Prolonged Bed Rest		Conventional Management	
Type	Patients	Av X Ray Cl Time Days	Patients	Av X Ray Cl Time Days
Uncomplicated	149	30 90	110	34 20
Recurrence	5 (2 6%)	54 00	44 (23.3%)	51 55
Other complications	38 (18 5%)	52 70	38 (18 5%)	52 00
Total	192	33 55	192	41 55

mostly crackling and occurred in showers near the end of inspiration Valuable information for controlling management was obtained from sedimentation tests performed weekly In the acute stage sedimentation rate is invariably elevated ranging from 20 to 40 mm per hour With improvement it gradually returns to normal and with recurrence or reactivation it shows secondary rises which can be correlated with clinical and x ray findings

Therapy in the acute stage of the disease was expectant and symptomatic Because of its effectiveness against secondary invaders sulfadiazine was given all patients with fever 102 F and higher Moderate cough and expectoration were considered a healthy physiologic reaction in the bronchitic and atelectatic aspects of the disease Therefore ammonium chloride was used as expectorant and sedative and narcotic cough mixtures were avoided Antipyretics were not prescribed routinely be

cause of loss of fluid and salt with the excessive diaphoresis and their depressing and debilitating action in some patients

It was noted that prolonged bed rest in the post febrile period greatly reduced incidence of recurrences (Table 3) A policy was then adopted to keep the patients in bed and isolated until sedimentation rate had decreased to 10 mm or less in one half hour Sedimentation rate also proved valuable as a guide to the appropriate time to begin the physical rehabilitation program rather than waiting until complete clearing of x ray and clinical findings It was noted that clearance was more rapid in patients with higher degrees of fever and higher white cell counts and that a rising leukocyte count was a good prognostic sign

[Cold agglutinin autoh maggh t m i) are found so often in the blood serum of patient with atypical pneumonia that their presence may be of some value in differential diagnosis The phenomenon may be so pronounced that reversible intravascular agglutination of the red blood cells may occur when the patient is exposed to cold Such a case with acrocyanosis was reported by Helvig and Freis (*Journal of the American Medical Association* 123 676 628 Nov 6 1943) They mentioned the possible hazard in using convalescent blood plasma or serum from patients who have recovered from atypical pneumonia This is timely in view of the occasional use of convalescent serum in treatment of the disease (see E M Solomon Human Serum Treatment of Atypical Pneumonia *Journal of Laboratory and Clinical Medicine* 29 493 499 May 1944)

An interesting study by Emerson Curnen Mirick and Ziegler (*Journal of Clinical Investigation* 22 695 697 September 1943) disclosed that in primary atypical pneumonia unlike pneumococcus pneumonia hypo amino acidemia does not occur and there is no significant tendency to retain salt and water in the acute stage or to excrete an excess in convalescence

S Moeschlin (Zurich) studied the blood picture in this disease and reports finding evidence of a lymphatic reaction On the sixth to eighth day this is indicated by the appearance of basophilic lymphatic cell form by the tenth to twentieth day increased lymphocytes are still present but they are normal in appearance with a narrow rim of protoplasm (*Schweizerische medizinische Wochenschrift* 73 540 1544 Dec 25 1943 —Ed]

Salmonella Pneumonia. Milton Gjelhaug Levine and Edward B Plattner (Univ of Illinois) report three cases

(5) Am J Cl P th 14 342 343 J 1944

of pneumonia in children in which pulmonary symptoms were primary and intestinal involvement was not noted clinically. Pneumonia was the diagnosis in each case before isolation of Salmonella suipestifer from the blood indicated the etiology of the infection. The three patients had antibodies in their blood against Salmonella suipestifer in high titers. They did not show agglutination titers against paratyphoid A or B organisms. Since the paratyphoid organisms alone are used in routine agglutination tests they might well be supplemented with the suipestifer strain to disclose otherwise undetected cases of suipestifer infection. Stool cultures were negative in the two cases in which they were made.

At a time when the pneumonias are being classified into typical and atypical groups it should be emphasized that many bacteria may cause pneumonia and that a cursory examination for pneumococci, Friedlander's bacilli and hemolytic streptococci may not eliminate the bacterial possibilities. Blood cultures and serologic tests must be used as adjuncts to careful bacteriologic examination of the sputum before atypical (assumed virus) pneumonia *is diagnosed by elimination.*

In the three cases sulfathiazole by mouth gave good results.

[A case of purulent pleurisy (chocolate-colored pus) due to salmonella infection was reported by Litmanovich and Grichener (*La semana medica* 51 14 17 Jan 6 1944) —Ed]

Allergic Pulmonary Consolidations O C Hansen Pruss and E G Goodman (Duke Univ) prefer this term to Loeffler's syndrome or some other deceptive name because there is no histopathologic evidence of an inflammatory or infiltrative process. They have observed six patients with the syndrome first described by Loeffler.

The syndrome consists of varying degrees of pulmonary consolidations at times multiple, often migratory and recognizable roentgenographically. It occurs in allergic individuals. Varying leukocytosis and eosinophilia are found and the clinical course is afebrile. *Persistent severe*

(6) An Allergy 2 95 108 M Ap 1944

asthma lack of response to the sulfonamides and history of frequent upper respiratory infections are characteristic The pulmonary changes are usually discovered by x ray examination the shadows are quite variable and may be mistaken for other condition In the authors patients pulmonary involvement suggested either bronchiectasis bronchopneumonia tuberculosis or sarcoid Differentiation of allergic pneumonic infiltration from bacterial pneumonitis (bronchopneumonia bronchiectasis with pneumonitis) is based on absence of fever or severe intoxication and the character of the sputum In virus pneumonia leukocytosis and eosinophilia are not present Ascariasis may simulate the condition confusion occurred in one patient who was then dewormed but the disease picture persisted Correct diagnosis of sarcoid is based on x ray findings of other abnormalities such as cystic areas in the terminal phalanges hyperproteinemia and often demonstrable skin lesions and lymph node involvement Eosinophilia of any marked degree is rare in sarcoid Differentiation from pulmonary tuberculosis depends on examination of the sputum which shows numerous eosinophils in a patient with allergic pneumonic response presence or absence of tubercle bacilli elastic fibers and Curschmann s spirals history clinical course and peripheral leukocyte response

The eosinophilia in the six patients was obviously of myeloid origin This may persist in moderate degree after disappearance of asthma and x ray evidences of pulmonary consolidation All patients gave a history of repeated upper respiratory infections and the acute episode appears to have been precipitated by a fresh respiratory infection The asthma always severe in these patients tends to persist until the pulmonary consolidation clears considerably or disappears allergic pulmonary consolidation should be suspected in all persons with intractable asthma and marked eosinophilia and leukocytosis Furthermore the peripheral blood of all patients with intractable asthma should be examined if leukocy

tosis and eosinophilia are found roentgenograms of the chest should be made to demonstrate or rule out presence *of pulmonary consolidation as the cause of therapeutic* failure

The patients were refractory to the usual forms of treatment including prolonged administration of oxygen helium and mixtures of the two Several patients were treated empirically by administration of pertussis vaccine *without benefit Sulfonamides are useful when there is* evidence of bacterial infection such as purulent bronchitis nasopharyngitis or sinusitis but they have no effect on the allergic pneumonic process and should be carefully used in these cases Aminophylline by mouth in combination with ephedrine sulfate 100 mg and phenobarbital *15 mg every four hours and rectal instillations* of 500 mg aminophylline in 60 cc water or suppositories of aminophylline (250 mg) were helpful in relieving the asthmatic distress in most patients However the therapeutic response is much slower than in the usual asthmatic patient Adrenalin was used rarely Aminophylline was given intravenously only to very ill patients without detectable evidences of myocardial embarrassment All patients were given salt water enemas daily as long as they were severely asthmatic Fluids were forced and fruit juices given in large amount Each patient received a mild sedative by mouth or rectally once or twice a day to allay anxiety and induce restful sleep Heroic measures are contraindicated Because of the prolonged asthmatic seizures patients with an allergic infiltration of the lungs particularly in private practice are given morphine or some similar alkaloid this is contraindicated because these drugs produce a contraction of smooth muscle and accentuate the bronchospasm

The authors *believe that the condition is an expression* of sensitization to nonspecific bacteria and that it can occur in constitutionally allergic individuals as well as in those who acquire the allergic response It is often a severe syndrome which may last for weeks but no

fatalities have been seen in patients with the condition

[This is one of the most sound and lucid articles published on a subject which has been exceedingly confused Some stress that th se consolidations are found in patient without asthma However thi is unusual and does not neces arily rule out the conception of an allergic phenomenon —Ed]

Tropical Eosinophilia Robert Heilig and S K Visveswar (Univ of Mysore) report on treatment with organic arsenicals Their two cases represented different degrees of the same clinical syndrome characterized by mild bronchial asthma leukocytosis eosinophilia and prompt response to neoarsphenamine In differential diagnosis trichinosis might have been considered since this is also characterized by leukocytosis and eosinophilia except for the facts that one patient was an orthodox Mohammedan and the other a strict vegetarian The condition is differentiated from Loeffler s syndrome by the fact that the lung infiltrations are not as transitory as in Loeffler s syndrome although both syndromes have many features in common Cases have been reported from the United States which form a connecting link between Loeffler s syndrome and tropical eo inophilia lasting from a few weeks to several months

An allergic origin of the disease seems possible especially in view of the fact that in none of the cases reviewed did the patients show signs or symptoms of the disease while staying in a particular area but developed them later confirming the fact that every allergen needs some weeks to sensitize the organ which manifests the allergic state

[A number of articles on tropical eosinoph lia have appeared in the Far East medical literature There is at least a reasonable upposition that many or most of these cases fall into the same category with cases described in the preceding report It has been customary in the Far Ea t to use arsenicals for treatment not for any specific effect but because they are supposed to desensiti e the pat ent —Ed]

Anaphylactic Nature of Rheumatic Pneumonitis Arnold R Rich and John E Gregory showed previously that cardiac and arterial lesions with basic characteristics

(7) I d Phy 2 305 311 S pt mbe 1943
(8) B ll J h H pk H p 73 465 470 Dec mbe 1943

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The authors believe that the condition is an expression of sensitization to nonspecific bacteria and that it can occur in constitutionally allergic individuals as well as in those who acquire the allergic response It is often a severe syndrome which may last for weeks but no

the cutaneous urticaria erythemas and purpura that occur in rheumatic fever Large basophilic multinuclear cells described by Gouley and Eiman in rheumatic pneumonitis were only occasionally found in the present series but they also occurred occasionally in sulfonamide anaphylactic pneumonitis Another point of interest is the finding of abundant eosinophils in the lesions in one case of each condition further supporting the view of an anaphylactic reaction

Chronic Indurative Pneumonia Resulting from Cardiospasm Case wth Nonpathogenic Acid Fast Bacilli in the Sputum is reported by Frederick C Warring Jr and Arnold B Rilance (Shelton Conn.)

Woman 65 who had a history of dysphagia and regurgi



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tation of food particles for 20 years developed weakness fever night sweats and cough with expectoration of mucoid

(9) J Lab & Cl M d 28 1591 1595 Octobe 1943

of acute rheumatic fever can be produced experimentally as a result of anaphylactic hypersensitivity Lederer and Rosenblatt and Merkel and Crawford pointed out that a peculiar focal pulmonary lesion occurs in some patients during treatment with sulfathiazole Rich has called attention to the fact that this lesion is primarily vascular and has presented evidence that it results from hypersensitivity to the drug

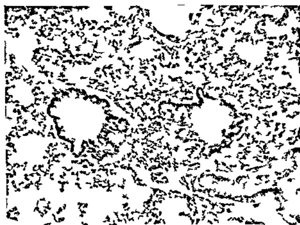
Based on these findings the authors compared the pneumonitis of hypersensitive origin in five patients without rheumatic fever with that in seven patients with rheumatic fever and acute cardiac lesions Five with rheumatic pneumonitis received no sulfonamides and two were given such small amounts of sulfapyridine that sulfonamide hypersensitivity could be ruled out The study revealed that the pulmonary lesions in rheumatic pneumonitis and in sulfonamide anaphylactic pneumonitis are basically identical histologically As in the case of rheumatic pneumonitis the primary pulmonary lesion in sulfathiazole hypersensitivity is a capillary damage with exudation of fluid and leukocytes fatal hemorrhages occur there is focal necrosis of the endothelium of the alveolar capillaries with thrombosis focal necrosis of the alveolar wall occurs a hyaline membrane lines some of the alveoli and no bacteria are demonstrable in the lesions by stain or culture As in the case of rheumatic lesions in later stages organization of some of the focal hemorrhages and exudates may occur The individual lesions of sulfonamide hypersensitivity tend to occupy a smaller area than do the rheumatic lesions This may be due to the fact that because of passive congestion of heart failure areas of pulmonary edema were present and passage of antigen and antibody through the pulmonary epithelium could be furthered in the rheumatic cases by this circumstance

Rheumatic pneumonitis appears to be the result of focal anaphylactic capillary damage and its characteristics suggest that it may represent the pulmonary analogue to

Dilatation of the lower end of the esophagu resulted in normal esophageal function and moderate clearing of the lung densities no acid fast bacilli were demonstrated in the sputum subsequently

[The chronic pneumonias in patient with cardiospasm may be suppurative as well as organizing and occasionally there is actually abscess formation in the lung Th pulmonary lesions depend obviously on the irritating qualitie of the aspirated food and fluid Some patients unaware of the cau of their difficulty take quan tities of mineral oil and this may explain chronic lipid pneumonia The pattern of the lesions often simulate tube culos s mycosi and other granulomatous lesion —Ed]

Sudden Death in Infants Due to Pneumonia John M Adams (Univ of Minnesota) points out that pneumonia is probably the most important single cause of sudden



F g 0—C 1 Sm ll d ll filt t d b h l s, w th ed ma ł h m h d g t

death in infancy He rep rt three ca e in infant with out previous evidence of illne s Two are given here

CASE 1 —Girl aged 3 month was found dead in her crib When seen earlier by the nur e he appeared well and had no fever Autopsy showed mall area of hemorrhage in the lung parenchyma frothy mucu The fluid exuding from the bronchi and no macroscopic area t con lidation Microscopically

(1) J P d t 3 1 J19 A g 194

sputum Roentgenogram of the chest is shown in Figure 18 Physical examination disclosed medium and fine rales over these areas A tuberculin test was positive Examination of the gastro intestinal tract showed the barium meal retained in the esophagus for 10 hours revealing obstruction of the car diac orifice The lower third of the esophagus was dilated there was no diverticula (Fig 19) Diagnosis was cardiospasm and chronic induration pneumonia caused by uncon scious aspiration of food probably during sleep

Two specimens of sputum raised from the lungs contained



Fig 19—Film 10 hou ft b ri m meal h ws d o p m

large numbers of acid fast bacilli morphologically similar to tubercle bacilli Further studies demonstrated the organi ms to be nonpathogenic acid fast saprophytes Skin tests with 0 1 mg tuberculin made from cultures of this saprophyte caused erythema 3 5 × 4 cm and marked induration indicating an acquired sensitivity to the nonpathogen in the sputum Of 12 positive reactors to OT with active tuberculosis only 2 re acted to 1 mg of this autogenou tuberculin. It is assumed that the nonpathogenic acid fast bacilli were derived from aspirated food particles similar organisms have been cul tured from raw fruit and vegetable

bodies in these cells The present cases showed no inclusion bodies but it is possible that sudden death preceded the formation of inclusions Absence of bacteria and almost complete lack of polymorphonuclear leukocyte response lend further support to the assumption of a virus etiology in these cases

Inhalation Pneumonia from Nitric Fumes Mortimer R Camiel and Henry S Berkan (Kings County Hosp Brooklyn) report two cases one of which is given here



Fig 22

Man 4) coppersmith and sheet metal worker always in good health on admission complained of headache and dizziness of one day s duration The day before he had assisted at welding without a mask and had been exposed to fumes from an acetylene torch from 7 00 a m to 4 00 p m with time out for lunch At 4 00 p m he went to the dispensary because of dizzines was given a gas to inhale and felt slightly better He had coughed since morning Dizziness increased to such an extent that during the night he was admitted by ambulance The welder he assisted also felt sick despite the fact that h had worn a mask

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the most significant finding was infiltration of small round mononuclear cells around the bronchial and bronchiolar system Other outstanding changes were diffuse hemorrhage in the alveolar spaces and thickened edematous septums Many small bronchioles appeared collapsed Some contained an epithelial cell exudate with no signs of bacteria or polymorphonuclear leukocytes (Fig 20)

CASE 2—Boy of 2 months was normal until the day before death when a slight nasal discharge and cough were noted At 3 00 a m the nurse found him extremely dyspneic



Fg 21—Ca 2 B nch w th ep th l l e date no polymo pho clea l Locyt o ba t h m h g edem and mall ro d cell ction.

and cyanotic and he died shortly afterward Autopsy findings were essentially the same as in Case 1 (Fig 21)

The three cases occurred in association with an epidemic of virus pneumonitis The most important and constant histopathologic change in all three patients i e interstitial mononuclear response in the alveolar tissues was also the predominant cellular response *in infants dying* of virus pneumonitis in mo t of whom death occurred the sixth or seventh day of illness In addition the latter cases showed proliferation and desquamation of bronchial and bronchiolar epithelium and cytoplasmic inclusion

Importance of Bronchography in Cases of Unresolved Pneumonia George S Grier III (Fort Eustis Va) tudied 40 cases which indicate the importance of bron chography and the fact that pneumonitis secondary to bronchiectasis is often misdiagno ed as primary atypical pneumonia Symptoms on admission in order of fre quency were cough mucopurulent sputum with oc casional blood streaking substernal soreness chills fever and sweats Examination revealed slight impairment of resonance suppressed breath sounds and fine crackling and coarse rales in the lower lobe of one or both lungs White blood cell counts showed slight leukocytosis but little increase in polymorphonuclear neutrophils The sputum did not settle into three layers in any case and no organisms predominated but those present were usually in the gram positive coccus group Roentgenograms dem onstrated stringy and mottled densities in the lower lobes usually unilateral and radiating out from the hilus toward the diaphragm Lateral films frequently revealed a pneumonic process behind the diaphragm or a cardiac shadow not seen in the postero anterior exposure After four or five days the acute febrile stage usually subsided and the cough abated with less sputum while suppressed breath sound and rales persisted or improved slightly Films at 7–10 day intervals showed little clearing

Bronchographic studies were done in cases in which resolution failed to occur in four to six weeks Iodized poppyseed oil wa injected into both sides even when the pneumonic process was unilateral Studies with iodized oil are contraindicated during the period of acute pneu monitis because they may aggravate the acute process

Procedure —The tip of a oft rubber catheter is placed in the piriform sinus as shown under fluoro copic examination n the lateral view The oil is injected after the patient has been placed in the desired position to outline a specific lobe Under fluoroscopic control the flow of the oil through the bronchi out into the alveolar space i observed Stereoscopic antero po ter or and oblique film are taken when both sides

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The patient was moderately dyspneic with shallow respirations and frequent nonproductive cough Temperature was 100 2 F blood pressure 135 70 pulse rate 100 per minute and respiratory rate 35 per minute There was a diffuse erythema over his face Many moist rales were heard over the lower halves of the lung fields Dizziness and headache disappeared the next day and after three days dyspnea and nonproductive cough Temperature varied between 99 and 100 6 F He was discharged the fourth day feeling fine

The roentgenogram (Fig 22) taken on admission showed a generalized submiliary pseudonodular infiltration throughout



F

both lungs The nodules varied from match head to pea size The changes were compatible with an acute exudative reaction with severe bronchiolitis and submiliary bronchopneumonia following inhalation of an irritant Further films showed regression of the nodular infiltration and a roentgenogram the day of discharge revealed almost complete subsidence of the findings A few residual infiltrations were still present in the right central lung field (Fig 23) Follow up study one month after exposure without recurrence of symptoms revealed complete absence of residual parenchymal changes

Association in London in November 1943 The voluntary immunization of tuberculin negative Norwegian nurses with BCG was begun in 1926 Among the vaccinated the annual incidence of tuberculosis has been 2 6 per cent and the mortality rate from it 0 2 per cent the corresponding figures for other nurses nonvaccinated and tuberculin negative on entry are 17 6 and 1 8 per cent Among vaccinated tuberculin negative medical students the incidence of tuberculosis has been 1 2 per cent as against 4 3 per cent among the nonvaccinated controls In Saskatchewan Canada where tuberculosis among the Indians is 10 times as common as in the European population Indian babies born in alternate years are being immunized with BCG using the others as controls Immunization is also available to all tuberculin negative nurses among whom as in Norway tuberculosis has in the past been unduly frequent The results of these efforts as far as they can be assessed are satisfactory The account by Muckenfuss of experience in New York City is also encouraging

From Great Britain Dalling reported field experiments of the Ministry of Agriculture now in progress on a large scale The method has been to immunize calves with BCG place them in heavily infected herds and examine them post mortem only after natural death or at the end of their term of usefulness Of 50 original animals 20 have been killed and only 3 had tuberculous lesions The experiment comprises thousands of cattle but its results will not be known for five years or more The vole bacillus vaccine has not been used in these experiments Wells however has given vole bacillus vaccine to three human volunteers who became tuberculin positive the only ill effect was a local abscess in one given probably an excessive dose

[Brooke and Day (Immunization with the Vole Acid Fast Bacillus against Experimental Tuberculosis *Bulletin of Johns Hopkins Hospital* 74 275 293 May 1944) concluded from experimental study in guinea pigs that the D15 strain of this bacillus significantly delayed the onset and diminished the severity of

are outlined If one side is studied a lateral may be substituted for the oblique view Postural drainage is instituted after the patient returns to the ward

Tubular and fusiform dilatations were the most frequent type of bronchiectasis demonstrated the saccular type was seen infrequently Of the 40 patients 31 had an initial misdiagnosis of primary atypical pneumonia and subsequently were found to have pneumonitis around a pre existing bronchiectasis Bronchographic studies should be made of all patients with pneumonia which fails to resolve in a reasonable period four to six weeks

[One should never be satisfied to dismiss a patient with a diagnosis of unresolved pneumonia. In almost all cases it is traceable to specific organisms which may be identified or to some pre-existing or associated structural damage to the lung or bronchi The responsible factor should be identified —Ed]

TUBERCULOSIS

Immunization against Tuberculosis According to an editor the mass of evidence testifying to the immunizing power of BCG in animals is overwhelming Still more effective is a living vaccine made from Wells s vole tubercle bacillus judging by the few experiments before the war of Wells in guinea pigs and of Griffith and Dalling in calves The degree of resistance in these experiments was striking amounting in calves almost to full immunity and encouraging the liveliest hopes for the future of this method Apart from apparent greater efficacy the vole bacillus vaccine has the important advantage that the bacillus is not a natural parasite of man and cattle Its virulence need not be artifically reduced and there is no danger of increased pathogenicity or of such diminution as to reduce its immunizing power it need only be maintained in its natural host to preserve its existing properties

In regard to human vaccination firsthand accounts of what is being done in Norway Canada and the United States were presented at a meeting of the Tuberculosis

(4) Brit M J 16 717 Dec 4 1943

Tuberculosis Survey of Freshman College Students H D Lees (Philadelphia) presents a report from the Tuberculosis Committee of the American Student Health Association concerning 7 452 freshmen from 12 eastern and southeastern colleges who were given tuberculin tests 19 4 per cent showed positive reactions As in earlier reports more male students reacted than female students Among the boys positive reaction numbered 21 3 per cent compared with 16 per cent among the girls This finding is of interest as the tuberculosis death rate among girls aged 15-19 is much higher than among boys in the same age group When both sexes are considered no significant difference is found in the percentage of positive reactions among freshmen graduated from private preparatory schools and those from public high school This is not in accord with the contention of certain educators that tuberculosis is less prevalent among students of private secondary schools A slightly higher percentage of positive reactions was found among girls from private preparatory schools than among boys who entered college from secondary schools of this type Positive reactions

POSITIVE REACTIONS IN FRESHMEN GIVEN TUBERCULOSIS TESTS

College	Total Records	Records Excluded	Total Tested	Pos. Reac.
All colleges	8 490	1 038	7 452	1 442 (19 4%)
Amherst	277	..	277	66 (23 8%)
Bennington	106	2	104	50 (48 1%)
Bryn Mawr	164	2	162	34 (21 %)
Penn State	2 091	63	2 028	450 (22.2%)
Princeton	690	3	687	100 (14 6%)
Rutgers	456	2	454	119 (26 2%)
Smith	638	365	273	24 (8.8%)
Syracuse	1 695	174	1 521	229 (15 1%)
Univ of Pa	838	284	554	167 (30 1%)
Univ of Va.	494	106	388	60 (15.5%)
Wake Forest	107	5	102	32 (31 1%)
Woman's College Univ of N C	934	32	902	111 (12.3%)

(6) Journal-Lancet 64 118 (Apr 1944)

infection with the human type of tubercle bacillus The vole bacillus vaccine was as effective as BCG and possibly superior The heat killed vole bacillus vaccine was found to be less potent—Ed]

Experimental Epidemiology of Tuberculosis The general belief is that human pulmonary tuberculosis is acquired by inhalation or aspiration of particles or droplets carrying tubercle bacilli Evidence suggests that the dimension of these objects must be much smaller than the lumens of the terminal bronchioles through which presumably the infectious units must pass for the disease to take root that the micro organisms are probably distributed in the air and that pure cultures of tubercle bacilli suspended in air could be killed by exposure to ultraviolet radiation Max B Lurie with Helen Tomlinson and Samuel Abramson (Univ of Pennsylvania) reports experiments to determine whether natural air borne contagion of tuberculosis can be prevented by ultraviolet radiation

The results show that ultraviolet irradiation of the air of a room exercises a protective influence against natural air borne contagion of tuberculosis in rabbits Radiant energy of low intensity reduces the incidence of tuberculosis considerably It completely protects rabbits of high natural resistance from acquiring demonstrable disease although they become tuberculin sensitive It fails to protect a small proportion of rabbits of low natural resistance from fatal tuberculosis When the radiant energy is of high intensity all rabbits whether of high or low natural resistance are almost completely protected from contagion so severe that it is fatal to most rabbits of the same genetic constitution not protected by these rays *The protected rabbits do not develop tuberculin sensitivity* The contagion of tuberculosis in these studies was air borne and the radiant energy exercised its protective influence by its bactericidal properties Ultraviolet radiation may *control air borne contagion of human tuberculosis*

(5) J F p Med 79 559 57 J 1944

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(6) J I La t 64 118 1 1 Ap 1 1944

were more numerous among girls from private schools than among those from public high schools In the case of the boys the percentage of positive reactions was some what higher among public high school graduates The size of the home community of the student seemed to be a negligible factor in the number of positive reaction

Ten cases of pulmonary tuberculosis were discovered five active and five inactive or healed In addition 18 freshmen presented x ray findings which warranted classi fication as tuberculosis suspects

Tuberculosis Case Finding by General Hospitals William G Childress A G Debbie and E L Harmon (Grasslands Hosp Valhalla N Y) report results of a tuberculosis case finding demonstration for unsuspected pulmonary tuberculosis by routine x ray or fluoroscopic chest examination carried out from July 1941 to January 1943 Of 9 693 persons admitted to the hospital or its out patient department 7 187 were included in the study Clinic patients were first examined by fluoroscope when evidence of disease was present roentgenograms were taken Routine roentgenograms of the chest on standard 14 × 17 in film were made for house patients

There was evidence of manifest tuberculosis in 290 or 4 per cent of these 201 or 2 8 per cent showed evidence of reinfection Forty two or about 0 6 per cent of the total 7 187 were classified as having active or questionably active lesions Activity was established in 25 of the 42 or approximately 0 35 per cent of the total number examined This group was classified after correlating the hospital or clinic record with the x ray findings A breakdown of active and questionably active disease shows the larger number of instances to be in men over 30 The ratio of males to females examined in these age groups was 3 2 ratio of yield about 7 1 This group is particularly important from a public health viewpoint because of the possibility of transmitting the disease

The authors believe that the opportunity offered by

(7) J A M A 12 1063 1065 A g 14 1943

routine x ray or fluoroscopic chest examinations of adults admitted to general hospitals as a source of tuberculosis case finding has not been fully utilized By discovering previously unrecognized cases of tuberculosis better protection is afforded the hospital staff

Pulmonary Tuberculosis Bacteriologic Examinations Supplementing Routine Thoracic Roentgenography in the Australian Military Forces are reported on by Reginald Webster (Melbourne) Of 1 548 recruits suspected of having pulmonary tuberculosis on the basis of roentgen evidence 364 were shown to be discharging tubercle bacilli (23 7 per cent) This figure was obtained by application of cultural methods and examination of gastric contents in the absence of sputum as against the number of 65 obtained by examination of smears of sputum alone A correlation of the roentgenologic and bacteriologic findings reveals that the proportion of positive bacteriologic findings is high (53 8 per cent) in the roentgenologically active group and declines through 14 3 per cent in the intermediate group of doubtful activity to 5 6 per cent in the group with roentgen signs suggesting an old inactive or healed process These findings confirm the efficacy of mass miniature roentgenography On the other hand a group of four recruits whose chest roentgenograms were negative were shown to discharge tubercle bacilli indicating the limitation of roentgenography The extended application of combined roentgenologic and bacteriologic investigation will no doubt result in detection of an ever increasing proportion of those pulmonary lesions which lie beyond the range of clinical perception

[One of the most important obligations is to evaluate tuberculous lesions discovered in mass surveys In many instances the seriousness of the les ons is underestimated because of their limited extent and symptomless manifestations Rare opportunities for effective treatment are sometimes lost —Ed]

Cold Hemagglutination Reactions in Tuberculosis Robert S Siffert and Benjamin Krautman (Kings County Hosp Brooklyn) performed cold isohemagglutination and

(8) M J A t l 61 67 J l 24 1943
(9) J Lab & Cl M d 29 270 72 M h 1944

autohemagglutination tests on a series of tuberculous patients. In none of these showing a positive cold iso-agglutination reaction was a high titer noted. This suggests that the cold iso-agglutination test may be valuable in differentiation of some forms of early tuberculosis from atypical pneumonia. Since positive reactions were found in low titer in tuberculous patients as well as in three



Fig 4.—P m y v rul t f ct on T p l ft n mal, a d r ght t o w k se al oe tg n g ms of th x of on a m l B tt m l ft m l d ght at n w k ntgen g ms of e sed l g f m r bb ts k ll l th m d te mp oe tg g am f rl l s t ro tg gr m f xc ed l ng obta d w th n h lf h r fte comp n roe tg g am f th ax. Labels on we k etc nd cat l p f tim aft t be l b ll h d b en j t d t a no ly C c l a n bottom l ft ca sed by l g b bl betwe l g d p p wh h t t l (M dl 195)

controls a test can be considered po itive for atypical pneumonia only if the cold agglutinins are present in high titer

[See editorial comment on van Raveisw av t al this YEAR BOOK p 172—Ed]

Comparison of Roentgenograms with Pathology of Experimental Miliary Pulmonary Tuberculosis in Rabbits E M Medlar C S Le queri and W H Ordway



F —S l g d f F gu 4 T p m l Left t p d bott m t tw w k ght t p d b tt m t th week

(Mount McGregor N Y) tudied primary infection with nonvirulent and virulent bovine tubercle bacilli and rein

(1) Am P T be 1 3 J l 1944

fection with virulent bacilli in rabbits The greatest amount and the essential nature of pathologic lesions were best determined by microscopy and in diminishing degree by macroscopic examination roentgenograms of excised lungs and roentgenograms of the thorax

In the animals primarily infected with virulent bacilli roentgenograms of the thorax showed the first definite though faint bilateral shadows three weeks after inoculation As the disease progressed the snowstorm effect on the film developed *rapidly with the intrapulmonary* shadows becoming larger and unequally more dense In the animals infected with nonvirulent bacilli, the greatest amount of disease observed was a rather faint snowstorm effect Some showed no definite evidence of pulmonary involvement one showed a slight haziness in the upper lung fields where a nontuberculous pneumonia was present and another showed tuberculous lesions more distinct and discrete but still of the soft type In the reinfected group first definite *evidence of shadows in roentgenograms* of the thorax was observed after three weeks Later there was great variation among the animals Generally by shadows alone single roentgenograms of the thorax failed to distinguish between primary infections with virulent and nonvirulent bacilli or between primary infection and reinfection with virulent bacilli Serial roentgenograms gave a clue to type of infection but not through the nature of the shadows per se Dense noncaseous caseofibrotic and fibrotic areas could not be differentiated in roentgenograms of inflated excised lungs Compact deposits of calcium recognizable by touch or by contact with a knife were clearly shown in caseous foci but with lesser deposits no differentiation between caseous material and calcium was shown *Superimposition of lesions caused a density in* shadows that did not indicate their true nature Compactness rather than size is the most important factor in determining whether a shadow of a focus will be cast Apparently the compact portion of a lesion must be equal at least to the volume of a primary parenchymal lobule before a

shadow will be cast in roentgenograms of excised lungs and shadows when first observed in films of the thorax indicate foci with considerably larger areas of compact inflammatory exudate This suggests that the loosely ar ranged periphery the so-called collateral inflammation may not cast a shadow and that the true size of a tubercu lous focus is not revealed roentgenographically If these facts are applicable to shadows in roentgenograms of the human chest the earliest demonstrable tuberculous focus would be a compact area of tuberculous bronchopneumonia which has all the spreading potentialities characteristic of any type of bronchopneumonia

[This study helps to establish in a scientific way the limitations of x rays in the d agnosis of small pulmonary lesions It seems necessary to re-emphasize the principle that x ray examination alone is not sufficient for sound diagnosis —Ed]

Carbolfuchsin in Propylene Glycol for Rapid Stain ing of Tubercle Bacillus The ability of propylene glycol to penetrate cellular structures and the fact that it is a com mon solvent for water lipids and various dyes suggested to Theron G Randolph and Robert F Mikell (Ann Arbor Mich) its use in staining of the tubercle bacillus

Method—To prepare stock solutions 1 Gm basic fuchsin is added to 100 cc propylene glycol (solution A) and 5 Gm phenol to 100 cc distilled water (solution B) Solutions A and B are combined in the proportion of 1 4 and this mix ture is shaken vigorously until completely mixed a process requiring only a few seconds The resulting solution appears to be stable as it has remained at room temperature for over two months without deterioration or variation in staining ability

The slide with the smear to be stained is immersed or flooded in the solution for a minimum of four minutes but may be left longer It is then washed with tap water de stained in acid alcohol and counterstained with methylene blue or brilliant green The decolorizing process requires 45-60 seconds and the counter tain is applied for a imilar period The organisms stain a bright red

Results obtained with this method were in agreement with those obtained with the Ziehl Neelsen stain In this medium the tubercle bacillus stains at room temperature

(2) Am R T be 49 109 J ry 1944

eliminating the heating process of the Ziehl Neelsen technic The absence of precipitated or dried dye on the slide permits a more rapid uniform and complete decolorization *reducing the possibility of error resulting from non* acid fast bacteria retaining the red stain

Clinical and Epidemiologic Significance of Rare Bacilli in Sputum has been studied extensively by F M Pottenger and J E Pottenger (Monrovia Calif) The technic used for microscopic demonstration of tubercle bacilli was the dilution flotation–picric acid method previously described by one of the authors This method supported by accurate *methods of collecting and preparing the specimen* and a search of at least 200 fields (10 minutes search) before declaring the specimen negative shows an average superiority of about eighty fold over the usual Ziehl Neelsen method Rare bacilli according to the authors technic may occur only once in 200 fields or even 400 fields but the finding shows that the patient is not actually bacillus free

The authors have found rare bacilli persisting in the sputum for long periods They conclude that if the patient is clinically well there is little danger either to himself or to others *from rare bacilli found by extremely sensitive methods* Sometimes large numbers of bacilli are temporarily discharged by one clinically well and carrying *on his work but he returns at once to the rare or negative* stage without reactivation of his disease Bacilli may persist in patients treated by physiologic methods alone or by *collapse procedures No method regularly produces a* continuously negative sputum The presence of rare bacilli in sputum does not necessarily indicate clinically active tuberculosis it shows that active tuberculosis has been present This finding may be consistent with good health and full working capacity Patients with rare bacilli are probably of greater danger to themselves than to those with whom they associate because bacilli are present in the tissues and may produce endogenous spread when the

(3) Am Rev Tuberc 48 9 9 November 1943

proper stimulus i pre ent \s for danger to others the number of bacilli expectorated is so small (in many cases a few hundred on ome days and none on others) that unless conditions are especially favorable for infection the number entering the tissues of others is insufficient to cause implantation The danger is probably greater to children than to adults and to the less resistant than to the stronger In it bearing on the problem of clinical tuberculosis the significance of rare bacilli in sputum is in much the same category as that of the tuberculin test A true appraisal depends on highly trained clinical judgment

[This interpretation of a commonly ob erved circum tance seems to be sound Howeve it houl l be emphasized that bacilli may be rare not at the r our e but only in the laboratory —Ed]

Acid Fast Bacilli in Patients of a Nontuberculous Medical Service E M Medlar W H Ordway and G S Pesquera (Mount McGregor N Y) on the basis of clinical and x ray interpretations classified 548 patients in three groups group I pulmonary field normal 60 8 per cent group II nontuberculous pulmonary lesions 26 6 per cent group III suggestive of tuberculosis 12 6 per cent Of the 69 patients in group III 33 presented lesions characteristic of a tuberculous infection but serial roentgenograms revealed no changes during hospitalization 15 showed den e parenchymal shadows in the lungs which were regarded as calcified tuberculous foci and 21 showed areas of haziness in apical and subapical areas

Acid fast bacilli were demonstrated in 6 5 per cent of the total series distribution in group I II and III was 4 2 7 6 and 16 per cent respectively pathogenic tubercle bacilli were found in 2 1 per cent of group I 1 4 per cent of group II and 8 7 per cent of group III All tuberculous patients with positive sputum smears had pathogenic tubercle bacilli in contrast to nontuberculous patients Ten per cent of the tuberculous patients failed to yield tubercle bacilli despite repeated inve tigations 31 of 74 patients who expectorated failed to show positive sputum mear and only 6 of the e failed to yield pathogenic

(4) Am R T I 48 304 313 N mb 1943

tubercle bacilli by repeated culture and animal inoculations Positive results were obtained in 15 of 24 subjects who did not expectorate Acid fast bacilli nonpathogenic by accepted procedures occurred with greater frequency in patients with pulmonary lesions tuberculous or otherwise than in those with normal lungs suggesting a possible etiologic significance of these organisms in pulmonary disease

Too great reliance should not be placed on positive sputum smears as shown by the fact that of 17 nontuberculous persons with 28 positive smears pathogenic tubercle bacilli were proved in only 4 The demonstration of tubercle bacilli in 2 per cent of subjects with negative chest roentgenograms suggests presence of occult tuberculosis and stresses its significance in search for immediate contacts in evaluation of new cases of tuberculosis and in differentiation between reinfection and superinfection'

Tuberculin Jelly Patch Test Donald Paterson[5] (London) uses a jelly consisting of 95 per cent OT and 5 per cent inert adhesive put up in small tubes After an area of skin between the shoulder blades is cleansed with acetone a small portion of the jelly is pressed out on the area Without waiting for the jelly to dry a 1 × 2 in piece of elastoplast is placed over the jelly and retained for 48 hours The patient must not bathe for this period After removal of the plaster the back is studied for several days A positive reaction is shown by an erythema or slight vesiculation of the skin in the shape of the marking used Paterson uses a V A negative result is shown by completely normal appearance of the skin area With the letter V the arms of which are ½ in long the reaction is equivalent to that of 0 1 cc 1 100 OT used in the intracutaneous Mantoux test

In 100 selected children the Mantoux and jelly tests agreed in both positive and negative results while the Vollmer patch test gave a lesser number for the positive and a greater number for the negative reactions than did

(5) B t M J 1 531 Apr 15 1944

both Mantoux and jelly tests Thus the tuberculin jelly test appears to be more accurate than the Vollmer patch test No unduly severe local reactions were noted Advantages are the much smaller cost of the jelly in comparison with the patches and the fact that the jelly will keep indefinitely in the tubes and is therefore more suitable for the general practitioner who uses such tests infrequently

Comparative Results with Transdermal (or Transcutaneous) and Intracutaneous Tuberculin Tests H J Corper (Nat l Jewish Hosp Denver) observed a striking parallelism when comparing the results of a transdermal tuberculin test prepared from an autolytic tuberculin and an intradermal test with purified protein tuberculin prepared from the same original bacillary cultures Among 103 patients tested 90 gave positive reactions to the transdermal test and 89 to the intradermal test Agreement between the two tests occurred in 82 of those giving positive reactions Among the 64 definitely tuberculous patients tested the agreement was 58 for the transdermal and 62 for the intradermal tests The slight differences were attributable to retardation of transdermal absorption in the definitely ill patients Among 39 nontuberculous subjects including those with possible infection but no evident tuberculous disease the agreement was again fairly close 32 reacted to the transdermal test and 27 to the intradermal test

The tuberculin test ranks among the best biologic diagnostic tests not as an exclusive test but rather as an inclusive one to verify other medical findings Even though highly specific these tuberculin tests are conditioned by a number of important factors not always controllable no matter what type of test is used The transdermal test has many advantages over any injection test because of the ease with which the test can be repeated if necessary Use of an intradermal test is warranted for verification at times but the transdermal test apparently is preferable as routine either for diagnosis or for surveys

(6) J Lab & Cl Med 9 39 403 Ap 1 1944

[The search for a simple and satisfactory tuberculin test continues and the accuracy of these newly devised tests will be studied with interest The Vollmer patch test now used widely in this country seems to be seriously undependable in the hands of some except as a preliminary test Lydia L Varbarg (*California and Western Medicine* 59 57-60 July 1943) reported a 25–50 per cent failure of the patch test to pick out reactors to tuberculin In Switzerland Braun (*Schweizerische medizinische Wochenschrift* 74 364 365 Apr 8 1944) has used a simple cutaneous application of Merieux s neotuberculin which is obtained from both bovine and human types of the bacillus It is doubtful whether this composition offers any advantage over other tuberculins—Ed]

Delayed Tuberculin Reaction. Marc Daniels' reports observations made during the Prophit tuberculosis survey A number of subjects who failed to react to either of the initial injections of tuberculin (0 1 cc OT 1 10 000 and 1 100) have several weeks later had a reaction at the site of the last tuberculin injection (1 100) It is of the same character as that normally visible in positive reactors *48–72 hours* after tuberculin injection and *leaves* a mark which may persist for several months as with a strong Mantoux reaction

In 14 cases the result of the last Mantoux test before the delayed reaction was negative and that of the test following the reaction was positive In all but one case the test after the delayed reaction showed a positive reaction to small doses of tuberculin (0 1 cc of 1 10 000 or less) *In three cases a primary focus was observed shortly* after the delayed reaction and in one case a diffuse shadow which may correspond to perifocal infiltration Of seven subjects who observed the delayed reaction five had other symptoms In one case symptoms (headache and fever) appeared four weeks before the reaction which may have corresponded to the primary infection If this is so this case shows the time lag between the infection and the development of allergy It is assumed that the delayed reaction in these cases occurs shortly after an infection and that the reaction to tuberculin still present in the skin occurs at the time tuberculosensitivity reaches a definite level

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In one case a delayed reaction occurred in a subject originally reacting only to OT 1 100 It appeared one week after fresh contact with tuberculous patients The subsequent Mantoux reaction was 2 plus to 1 10 000

[In rare ca es the tuberculin reaction may be delayed after the development of a tuberculous lesion This peculiarity is not well understood —Ed.]

Anemia and Sideropenia in Tuberculosis Pathogenic and Therapeutic Study is reported by Albert Reginster Anemia is a frequent almo t constant symptom of pul *monary tuberculosis Its intensity is variable rarely attain* ing serious proportions yet its presence should not be ignored It reduces general resistance interfering with systemic reaction against the tuberculous process Fur thermore because of accelerated circulation which ensues congestion near the lesions unfavorable to scar formation may develop

Seventy two males with tuberculosis of different degrees were treated with iron In the male adult the level generally regarded as normal is 120–150 micrograms of acid soluble iron per 100 cc plasma Two of these patients had normal iron content In 12 it varied from 100 to 120 micrograms and in all others it was below 100 micrograms Results of blood iron determinations suggested a definite relation ship between gravity of symptoms and sideropenia This was not absolute but in some relatively severe cases plasma iron was greatly reduced The cases showed definite cor relation between fever and lack of plasma iron To deter mine whether the fever could account for sideropenia three patients with a nerve affliction (generalized paraly sis) were given artificial fever treatment Plasma iron content was determined before and afterward and in all cases the values were reduced by induction of fever This finding permits the conclusion that fever may account for sideropenia in tuberculosis

Administration of iron to the e patients proved ineffec tive The tuberculous patient apparently does not absorb

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iron by mouth or by injections when the disease is progressive When the patient is in good condition and without fever iron is absorbed well in which case food will furnish a sufficient quantity to restore a normal level in plasma and hemoglobin

Nutritional Studies in Tuberculosis Prothrombin Deficiency and Vitamin K Jason E Farber and D K Miller (Univ of Buffalo) performed 437 prothrombin determinations on nonbleeding tuberculous patients and 116 on patients with bleeding and streaking Thirty three per cent of the nonbleeding and 53 per cent of the bleeding patients had a prolongation of the prothrombin time of three seconds or longer There was not always a correlation between the amount of bleeding and the prothrombin time Occasionally a massive hemoptysis occurred with a normal prothrombin time Daily prothrombin determinations were made on 26 patients whose prothrombin time was prolonged and who were receiving vitamin K (menadioné) Sixteen of these were bleeding In most instances the prothrombin time returned to normal within 24–72 hours in only a few patients with bleeding was it refractory to vitamin K Although the prothrombin time was restored to normal the patients often continued hemorrhaging particularly those with large hemoptyses On the other hand some of the patients with smaller hemoptyses stopped bleeding abruptly coincident with restoration of the prothrombin level The dose of menadione was 3 2 mg daily In nine controls with hemorrhage who had prolonged prothrombin time and did not receive vitamin K the prothrombin time did not return to normal until seven to eight days had elapsed

The prothrombin determination was arranged according to the clinical status of the patient Of 279 patients classified as having frankly active tuberculosis 44 per cent had an increase in prothrombin time while only 14 per cent of 158 classified as having inactive or quiescent lesions

(9) Am. Re T ber 48 406 410 D cemb 1943

had a similar increase Administration of sodium phenobarbital did not influence prothrombin time

Prothrombin deficiency in tuberculous patients should be considered as a part of a general nutritional deficiency Synthetic vitamin K is effective in restoring prothrombin concentration and should be given for this purpose only There is no evidence that it stops pulmonary hemorrhage or influences its course

Management of Minimal Pulmonary Tuberculosis Disclosed by Fluorography W D W Brooks reports that fluorography of 479 373 apparently healthy men of the Royal Navy showed that 6 077 had roentgen signs of adult type pulmonary tuberculosis In 47 9 per cent of these the lesion was minimal Of 23 344 WRNS 213 had similar evidence of tuberculosis with minimal lesions in 55 4 per cent of these Similar investigations among civilians will probably reveal large numbers of cases of pulmonary tuberculosis of this slight degree raising difficult problems of disposal and treatment In some of these minimal cases the disease is arrested or retrogressive but in others it is progressive Careful study is needed to decide whether the infection is active and investigation in hospitals is essential When 2 911 sailors with minimal lesions were first studied in the hospital 16 per cent showed evidence of active infection in 63 per cent the disease appeared to be inactive but stability of the lesions was doubtful In 21 per cent the disease was arrested

Navy personnel with apparently inactive minimal tuberculosis have been placed on light shore duties and kept under observation Study of these cases shows that the younger the patient the more likely is the disease to become active and the relapse to be serious

Diagnosis of apparently inactive minimal tuberculosis in males under 50 should imply outpatient supervision and regular inpatient re examination for the following two years For patients under 30 the observation period should probably be longer Supervision should be combined with

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iron by mouth or by injections when the disease is progressive When the patient is in good condition and without fever iron is absorbed well in which case food will furnish a sufficient quantity to restore a normal level in plasma and hemoglobin

Nutritional Studies in Tuberculosis *Prothrombin Deficiency and Vitamin K* Jason E Farber and D K Miller[9] (Univ of Buffalo) performed 437 prothrombin determinations on nonbleeding tuberculous patients and 116 on patients with bleeding and streaking Thirty three per cent of the nonbleeding and 53 per cent of the bleeding patients had a prolongation of the prothrombin time of three seconds or longer There was not always a correlation between the amount of bleeding and the prothrombin time Occasionally a massive hemoptysis occurred with a normal prothrombin time Daily prothrombin determinations were made on 26 patients whose prothrombin time was prolonged and who were receiving vitamin K (menadione) Sixteen of these were bleeding In most instances the prothrombin time returned to normal within 24–72 hours in only a few patients with bleeding was it refractory to vitamin K Although the prothrombin time was restored to normal the patients often continued hemorrhaging particularly those with large hemoptyses On the other hand some of the patients with smaller hemoptyses stopped *bleeding abruptly coincident with restoration of the prothrombin level* The dose of menadione was 3 2 mg daily In nine controls with hemorrhage who had prolonged prothrombin time and did not receive vitamin K the prothrombin time did not return to normal until seven to eight days had elapsed

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ibsequently unfavorable The lesions of the 40 pa given collapse therapy became inactive and have ed so

author holds that persistently positive sputum in sence of a parenchymal lesion is an indication for ollapse regardless of clinical symptoms physical r benign x ray changes Occasionally a small lesion charge its tubercle bacilli into a bronchus and pro- healing the sputum becoming negative The prac lue of au cultation should not be minimized Often rmination of rales will be the deciding factor as to lung requires collapse particularly with similar l x ray changes In early minimal tuberculosis and erately advanced cases with persistently negative bed rest brings favorable results If collapse therapy advisable the more conservative form should be st before apical thoracoplasty is planned

ence and Treatment of Tuberculosis in Children ussed by G B Fleming (Royal Hosp for Sick h Glasgow) Of 100 consecutive patients with ous meningitis hospitalized between April 1939 tober 1942 80 had primary lung infection and 6 abdominal infection while the primary focus in not determined As tuberculous meningitis is the erminal event in children dying of tuberculosis it that infection of the respiratory tract is the main f death from tuberculosis in children Such infec least in fatal cases arises from human contact ildren sooner or later become infected with tubercu Vith the tuberculin test as an indicator it has been that only a small proportion of those under 1 year have infection as age increases positive skin reac become more and more frequent so that at age 12 cent and at age 20 70 per cent have positive reac Many children recover completely and many pass h this primary infec ithout symptoms In a however on progresses and in

appropriate modifications in the patient s mode of life Opportunities for industrial convalescence as typified by the Altro Work Shops in the United States may be needed Availability of such facilities over a wide range of indus tries would insure essential training continued selected employment financial stability and maintenance of high morale during the critical years in the lives of these patients

[Some well organized plan for the observation of minimal lesions should always be put into effect (see Webster this YEAR BOOK p 195) —Ed]

Management of Minimal and Moderately Advanced Pulmonary Tuberculosis Arthur Rest[a] (Spivak Colo) presents a study of 155 patients—23 with minimal and 132 with moderately advanced lesions The observation period included residence at a sanatorium and a 1–10 year follow up period

Twenty one of the 23 patients with minimal lesions were treated by six months or more of bed rest On admission 1 had positive sputum and 20 negative The former had intestinal tuberculosis which later proved fatal The sputum of the other 20 was still negative on discharge The lesions of two became progressive later and those of the remainder are still inactive Two patients with minimal lesions received collapse therapy—one a phrenic nerve operation because of streaking the other artificial pneu mothorax because of progression Both cases are inactive

Of the 132 patients with moderately advanced lesions 92 were treated by six months or more of bed rest Twenty seven had positive sputum on admission of these only 14 had negative sputum on discharge Forty of the 132 pa tients were treated by collapse Of the 14 on whom phrenic nerve operations were done 11 had positive sputum on admission 8 of these had negative sputum on discharge Of the 20 treated with pneumothorax 17 had po itive sputum on admission 15 of these had negative sputum on dis charge Seventy three of the 92 patients treated by bed rest alone had inactive lesions on discharge The course of 15

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was subsequently unfavorable The lesions of the 40 patients given collapse therapy became inactive and have remained so

The author holds that persistently positive sputum in the presence of a parenchymal lesion is an indication for early collapse regardless of clinical symptoms physical signs or benign x ray changes Occasionally a small lesion will discharge its tubercle bacilli into a bronchus and proceed to healing the sputum becoming negative The practical value of auscultation should not be minimized Often the determination of rales will be the deciding factor as to which lung requires collapse particularly with similar bilateral x ray changes In early minimal tuberculosis and in moderately advanced cases with persistently negative sputum bed rest brings favorable results If collapse therapy becomes advisable the more conservative form should be used first before apical thoracoplasty is planned

Incidence and Treatment of Tuberculosis in Children are discussed by G B Fleming (Royal Hosp for Sick Children Glasgow) Of 100 consecutive patients with tuberculous meningitis hospitalized between April 1939 and October 1942 80 had primary lung infection and 6 primary abdominal infection while the primary focus in 14 was not determined As tuberculous meningitis is the usual terminal event in children dying of tuberculosis it follows that infection of the respiratory tract is the main cause of death from tuberculosis in children Such infection at least in fatal cases arises from human contact Most children sooner or later become infected with tuberculosis With the tuberculin test as an indicator it has been found that only a small proportion of those under 1 year of age have infection as age increases positive skin reactions become more and more frequent so that at age 12 50 per cent and at age 20 70 per cent have positive reactions Many children recover completely and many pass through this primary infection without symptoms In a certain number however the infection progresses and in

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these the terminal picture is characterized by a fatal miliary spread and tuberculous meningitic involvement

Positive Mantoux reactions have a much less grave significance in older children than in younger children or in infants The incidence of tuberculous meningitis falls with increasing age Of 326 children dying of tuberculous meningitis at the hospital between 1931 and 1943 70 per cent were under 4 years (see Table) Of a series of children admitted with positive tuberculin reactions 286 were under 4 years and one third of these died of tuberculous meningitis 322 were over 7 years and only 5 per cent of these died of tuberculous meningitis

AGE INCIDENCE OF TUBERCULOUS MENINGITIS

AGE Y	CASES	OF T L		AGE YR	CASES	OF TOTA
0–1	66	20 24	70	7– 8	7	2 14
1–2	81	24 84		8– 9	12	3 68
2–3	48	14 72		9–10	6	1 84
3–4	33	10 12		10–11	4	1 2?
4–5	28	8 59		11–12	8	2 44
5–6	20	6 10		12–13	1	0 30
6–7	12	3 68				

These findings emphasize that most children are infected with tuberculosis from a human source and that the younger the infected child the greater the risk to life Therefore young children should be shielded from contact with persons with open tuberculosis Children under 4 with positive tuberculin reaction should be placed in suitable surroundings and kept under observation for about six months

Administration of 4 2-Diaminophenyl 5-Thiazolesulfone (Promizole) in Tuberculosis Promizole is an isostere of 4 4 diaminodiphenylsulfone soluble in water at pH 6 5 and 28–30 C to the extent of 30–40 mg per 100 cc It is readily soluble in dilute acids acetone dioxane and dilute (70 per cent) ethanol and moderately soluble in absolute ethanol ethyl acetate and ether Molecular weight is 255

W H Feldman H C Hinshaw and F C Mann used

(4) P oc Staff Me t M y Cl n 19 5 33 J 26 1944

126 guinea pigs in two experiments Forty two guinea pigs were used in the first experiment divided into three groups of 14 each (1) controls (2) to receive 4 4 diaminodiphenylsulfone (3) to receive promizole Feed for groups 2 and 3 contained 0 5 per cent by weight of the respective drugs for six days then promizole was increased to 1 per cent Nine days after medication was begun all animals were inoculated subcutaneously with 0 1 mg of an 18 day culture of tubercle bacilli Medication was continued in groups 2 and 3 until the sixtieth day after inoculation when all surviving animals were killed Relative effectiveness of the two drugs was determined by histologic examination of spleens livers and lung Comparison of tuberculous changes in the controls and treated animals showed strikingly less tuberculosis in the latter (see Table) In a second experiment the disea e was likely

AVERAGE SEVERITY OF TUBERCULOSIS IN DIFFERENT ORGANS EXPRESSED NUMERICALLY

G o	S le n (Max 35)	Lungs (Max 30)	Live (Max 25)	Av Index In ection (Max 90)	Bloo Co cen tration Mg pe 100 C	H m lobin Gm 100 Cc
1	31.8	16 4	18 2	66 6		Not done
2	1.3	1 8	1 3	4 4	?1	12.2
3	1 9	2 2	2 1	6 2	4 9	10 1

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to be well established before administration of the drug was started Therapeutic efficacy of promin and promizole was compared Twenty controls received no medication 20 were given promin and 20 promizole 6 weeks after infection and 13 were given promizole 10 weeks after infection and 15 promizole 14 weeks after infection The experiment was continued 226 days after inoculation with tubercle bacilli when surviving animals were killed Although 80 per cent of controls were dead only 13 (19 per cent) of all animals in the other four groups had died Of these four died before treatment started or before lapse of a minimal treatment period of 30 days

Promizole seems reasonably well tolerated by guinea

pigs when given by mouth for a prolonged period Some blood dyscrasia occurred but changes were not critical and were reversible A daily dose of 200–250 mg promizole had a therapeutic efficacy comparable to a daily dose of 400–500 mg promin and was capable in the dosage used of exerting a favorable influence even though treatment was not started until 6 10 or 14 weeks after inoculation Prolonged administration of promizole induced diffuse parenchymatous hyperplasia of the thyroid which was reversible when the drug was withdrawn

H C Hinshaw W H Feldman (Mayo Clinic) and K H Pfuetze[6] (Cannon Falls Minn) administered promizole to 56 patients with tuberculosis Approximately a third received sufficiently large doses to attain blood concentrations comparable to those adequate to control tuberculosis in guinea pigs Preferred dosage is 10–16 Gm daily orally No serious toxic results were noted from this dosage though treatment in some instances was continued four months These quantities yield concentration of 1 5–4 2 mg per 100 cc blood (average 2 6 mg) Promizole appears in urine in rather large amounts usually over 80 per cent indicating relatively complete absorption Promizole has demonstrated little if any hemotoxic properties prominent in diaminodiphenylsulfone promin and diasone which have a favorable effect on tuberculosis Slight and transient cyanosis was noted occasionally With large doses there is evidence of slightly increased blood regeneration A mild toxic erythema rash probably due to promizole was noted in two instances systemic symptoms were slight and the eruption promptly faded when treatment was discontinued No instances of leukopenia drug fever or other idiosyncrasy hematuria or other evidence of renal damage or serious gastro intestinal disturbances were observed

Clinical results cannot be evaluated at this period of study The trend toward spontaneous healing is frequently observed furthermore healing mechanisms in tuberculosis

(5) P St ff M t M Cl 19 33 36 J 26 1944

act slowly and are unlike those noted in acute diseases responding to chemotherapy There is also no quantitative measure of activity of lesions such as serologic tests afford in syphilis Accurately controlled studies will be required before this or any other therapeutic agent can be evaluated in pulmonary tuberculosis and patients should be offered no hope of immediate prospects of simplified therapy

Chemotherapy of Clinical Tuberculosis with Promin H Corwin Hinshaw Karl H Pfuetze and William H Feldman report on the clinical course up to December 1943 of 36 patients who first received promin for tuberculosis during 1941 The patients were divided into four groups on the basis of degree of improvement

Group 4 consisted of eight patients showing marked improvement All showed consistent striking and unexpected improvement while receiving chemotherapy In five the disease was far advanced and in three moderately advanced Six of the eight have consistently negative sputum Clinical improvement has continued in all cases at least during promin administration One patient left the sanatorium markedly improved but against medical advice a slight extension of the disease has apparently been controlled by further treatment In six patients the disease is definitely arrested and five of these are working The only patient with consistently positive sputum had a huge cavity and considerable fresh tuberculosis when treatment was begun Treatment was continued for a little over a year with rapid clearing of exudative lesions but there is still a large cavity with no other roentgen evidence of active disease her general condition has deteriorated during the past year All patients in the group received relatively large doses of promin well in excess of average toleration

Group 3 included six patients with moderate improvement All have continued to improve with arrested disease and negative sputum except for one who died after thoracoplasty Of eight patients in group 2 with slight improve

(6) Am R T b 50 5 57 F b 1944

ment two have been dismissed with the disease arrested collapse therapy was instituted in one and the original lesion in the other was not extensive The four others who had mo t extensive destructive di ease involving large portions of both lungs have made excellent progress aided in two cases by thoracoplasty Two patients made no progress and appear worse Eight patients of group 1 with no improvement have shown no change in their clinical condition despite chemotherapy One patient with a lesion of bronchostenotic type improved sufficiently to be dismissed and has had negative sputums since March 1943 Two other patients received surgical collapse and progressed satisfactorily The remaining five have shown no significant change except for one who died of pulmonary hemorrhage

Two patients reported on previously have had extension of the disease Chemotherapy was continued in both and the disease appeared to be under control One of the patients is working with an arrested condition the other had temporary arrest of the disease for eight months but later had extension when treatment was discontinued and she worked She is again improving and receiving chemotherapy Four patients with extensive hopeless disease receiving chemotherapy during terminal stages had died at the time of the previous report

Generally results have been sufficiently suggestive to demand study of many cases carefully controlled to confirm or deny these preliminary impressions on a small group Exudative lesions of recent origin appear to be more promising for chemotherapy than those which involve caseation necrosis cavitation and fibrosis The toxic manifestations of promin and related drugs must be considered but they are measurable reversible and controllable and apparently have no adverse effect on the clinical course of tuberculosis

[During the past year another preparation diasone (disodium formaldehyde sulfoxylate diaminodiphenylsulfone) has been subjected to experimental and clinical study for its effect on tuberculo is (G W Raiziss *Science* 98 350 Oct 15 1943) It inhibits

tle lisca e much the same as the other preparations described However it is not free from toxic effects some of which may be severe and occasionally fatal (K H Pfuetze and M J Pyle Severe Reaction Following Administration of Diasone *Journal of the American Medical Association* 125 354 355 June 3 1944) Petter and Prenzlau (*Illino s Medi l J urnal* 85 189 196 April 1944 *American Review of Tuberculosis* 49 308 3_? April 1944) have reported clinical observations Unfortunately reports on diasone in the lay press have been confused and open to misinterpretation much to the di appointment of many patients The Committee on Therapy of the American Trudeau Society published a statement (*American Review of Tuberculosis* 49 391 39? April 1944) emphasizing that the curative value of these drugs in tuberculosis in human beings cannot be estimated even tentatively on the data so far made available The studies are still in the investigative stage and human beings have not been found to respond in the same way as guinea pigs A number of other chemotherapeutic studies on drugs of different nature are being carried out by various workers—Ed]

Determination and Treatment of Pressure Cavities in Pulmonary Tuberculosis Arthur M Vineberg and Walter E Kunstler (Montreal) state that consideration of some of the factors responsible for cavity formation and closure shows that the condition of the draining cavity bronchus must be known before surgical collapse therapy is attempted This information is obtained only through complete study of the intracavitary pressures Readings should be taken of all cavities larger than 2 5 cm prior to thoracoplasty If the pressure indicates presence of a tension cavity then thoracoplasty should not be done as an initial measure as residual cavities may remain A tension cavity should be treated first by intracavitary suction drainage atmospheric or negative pressure cavities should be treated by thoracoplasty

Special instruments for these procedures were designed by the authors A 16 gage Kuss initial pneumothorax needle is fitted with Luer Lok connections including a blunt stilet insuring an air tight system On the shaft of the needle there is a sliding collar which can be fixed at any point by a thumb screw The exploring needle consists of a 19 gage shaft 12–18 cm long the hub of the needle can be attached to the shaft at any point by a screw

(7) S g Gy & Ob t 78 245 74 Ma h 1944

lock which contains a small rubber washer and makes an air tight connection with the hub The length of the needle shaft required is measured by a steel ruler Two metal cannulas designed by Wangensteen for drainage of lung abscesses are modified to take a Luer Lok hub at the noncutting end the hub fitting both cannulas

TECHNIC —In patients with cavitation referred for thoracoplasty either there has been inefficient pneumothorax with adherent apex or it was impossible to induce pneumothorax Even though the pleural space directly over the cavity appears obliterated there may be small residual areas in which the parietal pleura is not adherent To determine intracavitary pressure under local anesthesia the Kuss needle with its trocar is introduced through the intercostal space down to the parietal pleura The trocar is removed and replaced by the blunt stilet connected to a 2 cc Luer Lok syringe The parietal pleura is punctured and a manometer attached to the side arm of the instrument by a rubber tube If a free pleural space is found the needle is immediately withdrawn and reintroduced at another point When the pleural space is obliterated and no pressure reading is obtained the sliding collar on the Kuss needle is set The Kuss needle is thus always kept at the same distance as regards both pleural space and cavity The distance from chest wall to cavity previously estimated by tomography is added to the distance from chest wall to hub of the Kuss needle thus giving the approximate length of exploring needle required This length is measured on the shaft of the exploring needle and the hub is set at the desired point by the adjustment on the lock screw The hub of the exploring needle is then attached to a three way stopcock also connected to a syringe containing saline and to a manometer The exploring needle is introduced through the Kuss needle until the lumen of the cavity is entered As the exploring needle penetrates the chest and cavity wall the stopcock must be turned in the direction of the syringe The plunger of the syringe is constantly being withdrawn as the needle is pushed ahead to protect blood vessels and to determine when the cavity lumen has been entered When the needle enters the cavity lumen there is either sudden release of resistance or entrance of air into the saline filled syringe As soon as air enters the syringe the stopcock on the exploring needle is immediately turned to obtain manometric readings thus little air is withdrawn and none escapes The patient is permitted to quiet down before pressures are recorded They are recorded in the following order initial

pressure quiet breathing after cough and pres ure following withdrawal and after introduction ot air The record of the cavity needling is kept on a special torm By taking the high est and lowest manometer readings a mean average ascer tains into which group the cavity belongs negative pressure atmospheric pressure or positive pressure cavity

For closed transthoracic intracavitary drainage the hub of the exploring needle is removed after pressure readings are taken and the Kuss needle is withdrawn A 20 gage spinal needle with syringe filled with saline is used to examine the region adjacent to the exploring needle to determine presence of blood vessels The spinal needle is always inserted directly into the cavity done over an area slightly larger than the largest cannula to be inserted The skin and subcutaneous tissue are incised about 0 5 cm on either side of the explor ing needle The active coagulating electrode is applied to the needle shaft for about _0 econd The cutting half of the medium sized Wangensteen cannula is then slipped over the shaft of the exploring needle and pushed into the cavity The needle is withdrawn and the active coagulating electrode again applied The second half of the medium sized cannula with its attached Luer Lok adapter is connected to the first half The intracavitary pressures are taken again to insure that the cannula is within the cavity There is usually an audible exchange of air after the cannula is introduced The adapter is removed and the cutting half of the large cannula is passed over the first cannula and pushed through the chest wall into the cavity The first cannula is removed and the upper half of the large cannula attached. The coagulating current is again applied to this cannula and the pressure readings are taken The upper half of the cannula i un screwed A size 14 Nelaton catheter is used Two extra holes of good size are cut in the catheter wall near the tip while a piece of linen thread is tied around the catheter This is placed at a distance from th tip so it will be flush with the skin when the tip is in the cavity The catheter is introduced through the cannula and the cannula is then removed One silkworm stitch closes the skin The tube is held in place by tape tied around the tube to the linen thread marker both ends of the tape are fixed to the skin by adhesive The dress ing is kept in place by a special binder including a change able piece of washed x ray film During the first 48 hours the catheter is aspirated with a 20 cc syringe three time daily If there is no blood streaked sputum suction is applied to the catheter either by intermittent negative pressure or constant pressure produced by a water steam or electric pump

Suction is usually maintained 12 hours daily discontinued at night and as the cavity grows smaller its strength is gradually decreased The catheter is left in place for at least 10 days End of treatment is determined by complete disappearance of the cavity as proved by tomography absence of tubercle bacilli in catheter contents and negative sputum If the positive sputum comes from another source suction drainage is discontinued and immediately supplemented by thoracoplasty The catheter is withdrawn slowly over three or four weeks in many cases it is slowly pushed out by the contracted lung

The authors report that in 150 cases cavities were needled and 27 were drained without a single complication of hemorrhage pleural empyema spontaneous pneumothorax or air embolism A combination of transthoracic intracavitary suction drainage and thoracoplasty produces the ideal in treatment of tension cavities namely a maximum collapse of diseased areas with minimal damage to normal lung parenchyma

Survival Rates in Pulmonary Tuberculosis In a previous communication Brian C Thompson[8] described an investigation of 406 adults with sputum positive tubercu

TABLE I

Yr Following Diagnosis (x)	Probability of Surviving Each Yr (px)	Probability of Dying Each Yr (qx)	No Alive on Each Anniversary Out of 1 000 Patients (lx)	No Dying Each Yr. (dx)	Probability of Surviving a Further 5 Yr ($5p_x$)
0	0 60	0 40	1 000	400	0.27
1	0 72	0.28	600	168	0.37
2	0 85	0 15	432	65	0 46
3	0 83	0 17	367	62	0 51
4	0 88	0 12	305	37	0 56
5	0 83	0 17	268	45	0 52
6	0 91	0 09	223	20	0 62
7	0 93	0 07	203	14	0 68
8	0 91	0 09	189	17	0 73
9	0 81	0 19	172	33	0 81
10	1 00	0 00	139	0	1 00

losis this group representing all persons with such a diagnosis in the entire population of a compact industrial area in 1928–1938 The investigation had continued for two

(8) B t M J 2 721 Dec 4 1943

more years and some of the patients previously lost from observation have been traced Table 1 presents a life table based on the proportion of patients who survived each individual year from the date of diagnosis and applied to a standard of 1 000 patients The chance of a five year survival on the day of diagnosis is approximately 1 4 improving to 50 50 if the first three years are survived

Though no patient died after surviving 10 years nearly half of those who were alive after the first 5 years failed

TABLE 2

	10 19 Y	20 29 Y	30 39 Y	40 P Y
No of patients	87	148	95	76
Probability of surviving 5 yr	0 20	0 26	0 35	0 21

to survive the second 5 On the basis of the present findings a 10 year survival should be a fairly reliable criterion of cure Though even in the ninth year almost one fifth of those who were alive at its onset failed to see its end the few survivors reached the fifteenth year

An additional analysis was made to determine the prognostic effect of sex and age The probability of a five year survival for the 211 males was 0 26 for the 195 females 0 25 Table 2 shows an analysis by age groups

Tuberculous Stenosis of Major Bronchi Mack McConkey and Joseph Gordon (Ray Brook N Y) report on 95 adults with pulmonary tuberculosis and tubercle bacilli in the sputum without evidence of collapse of the lung Of these 61 had persistent rhonchi unrelieved by cough with 8 in the incipient 22 in the moderately advanced and 31 in the far advanced stage The complication was considerably higher in women than in men (39 22) In 58 diagnosis of a stenotic lesion of a major bronchus was verified by bronchoscopy after being suspected because the rhonchi were more readily palpable and loudest over the stenotic bronchus In certain cases rhonchi are best elicited when the patient is lying on the side of the affected bronchus

(9) Am Rev T be 49 140 145 F b y 1944

with the shoulder depressed Demonstration of rales is also helpful for elicitation of rhonchi and should not be omitted if the complication is suspected In the remaining three patients the bronchial tree was normal bronchoscopically Of the 34 patients without rhonchi 32 showed no disease of the major bronchi bronchoscopically in 2 there was localized inflammation of the main bronchus and in 1 of these a very small ulcer Analysis of these 34 cases suggests that with few exceptions stenosis of a major bronchu may be excluded in absence of persistent sonorous rhonchi

Bronchosoepy permitted classification of the lesions by their surface appearance localized bronchitis ulcerative lesions hyperplastic granulations and fibrostenotic lesions Localized bronchitis was commonest occurring in 25 of the 95 patients The intact mucosa presents a localized area of redness and swelling and bleeds readily from slight trauma Spontaneous healing occurred in a number of these cases accompanied by disappearance of rhonchi In others the lesions have become ulcerative and in still others retrogressive ulcerative lesions eventually appeared as localized areas of inflammation

Roentgen Changes in Esophagus in Tuberculous Mediastinitis Differential diagnosis of mediastinal tumor and mediastinal infection is often difficult because the only roentgen sign may be widening of the mediastinal shadow without parenchymal lung disease Lloyd E Hawes (Massachusetts Gen l Hosp) confirmed the value of studying the barium filled esophagus in addition to the usual chest films in five patients with active adult mediastinal tuberculosis In two actual involvement of the esophageal mucosa was present and in all the roentgen appearance of the esophagus had changed Figure 26 shows significant changes in each case The tracings were made from spot films taken during roentgenoscopy in the posteroanterior projection The segment of involved esophagus was adjacent to the enlarged nodes or inflammatory mass

Esophageal displacement by soft tissue masses and pres

(1) Am J Roentgen 51 575 584 M 1944

sure defects on the lumen were seen in three cases Esophageal mucosa in two cases showed irregularity of normal pattern In one autopsy showed a large tuberculous ulcer of the esophagus In another a tuberculous sinus ran from a small esophageal diverticulum into caseating mediastinal nodes In another mucosal irregularity was so marked that ulcerations of a carcinoma were simulated Esophagoscopy however showed no mucosal abnormality The irregularity may be due to folding and kinking of the wall and mucosa by scarring and small inflammatory

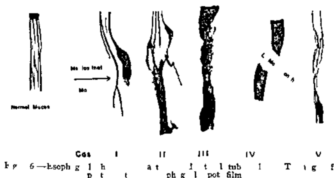


Fig 6—Esoph g l h a t l t l tub l T i g f p t t ph g l pot film

masses The involved wall varied in width in four cases when the lumen was filled with barium In some places the lumen was narrower than usual In one case the lumen when stretched out failed to collapse normally during contraction The stenosis is due to pressure of inflammatory masses or scarring the stretching out is probably the result of adhesions A fistula was demonstrable in one case and found at autopsy in two others

Four cases showed a number of projections appearing as points or rounded waves from the involved segment of the barium filled esophagus In one case the projections were so numerous that a fine wavelike outline was given to the esophagus They were not transitory If in one spot roentgenogram a peristaltic wave is photographed a rounded projection of the wave is seen but in subsequent

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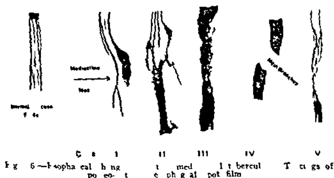
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C e I II III IV V

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roentgenograms the same wave is not seen However the projections in these four cases were in the same position from film to film and after several hours when the patient was examined in the same postion Size and shape of the projections could be varied by the degree of barium filling



Fig 27 (left) —Spot film Not p nts of atta hme t f adh s to wall (r ows)
Fig 28 (gbt) — Spot film W th le s fill g fis t l en M c s l pat tern n w dened area is egula

These projections are probably related to scarring and adhesion formation in the periesophageal tissues and are analogous in etiology to traction and Fleischner divertic ula and probably curling Projections in the esophagus of a young person have considerable differential diagnostic significance In a boy 16 their discovery localized the cause of obscure fever to the mediastinum when other roentgen and clinical studies had failed (Figs 27 and 28)

With signs of active infection and within mediastinal widening their demonstration strongly suggests mediastinal infection rather than tumor Operative trauma must be excluded

Amyloidosis Complicating Tuberculosis Diagnosis Prognosis and Treatment Samuel Cohen (Rochester N Y) reports on 79 fatal cases of tuberculosis complicated by amyloidosis In 53 diagnosis of amyloidosis was proved at autopsy In 143 cases of tuberculosis autopsy disclosed an incidence of amyloidosis of 39 per cent In 26 of the 79 cases there were clinical evidence of amyloidosis during life and 100 per cent absorption of congo red dye Autopsy was not done in this group

Seventy seven patients had progressive pulmonary tuberculosis of varying degree with cavitation in one or both lungs Many had also extrapulmonary involvement particularly of the larynx and intestines Only two had arrested disease at the time of death Fifteen had empyema by contrast 8 of 88 patients without amyloidosis were found at autopsy to have empyema The liver was enlarged in 46 patients the spleen in 18 Dependent edema was a common clinical sign Anemia of varying degree was present in 67 patients The commonest laboratory findings were decreased plasma proteins decreased albumin globulin ratio and elevated blood cholesterol

Renal involvement was present in 45 of the 53 cases The commonest urinary signs in patients with amyloidosis were albumin and casts Their presence even in the absence of other confirmatory data strongly suggests amyloidosis provided tuberculosis of the kidney is excluded Repeated congo red tests were performed on 62 of the 79 patients Thirty seven had 100 per cent dye retention in one hour Proteinuria and casts preceded the first positive dye tests in seven of these Twenty five had less than 100 per cent retention Eighteen had albuminuria and casts

Using appearance of albuminuria and casts to indicate the probable onset of amyloidosis Cohen evaluates by

( ) A I t M d 19 990 100 D mbe 1943

means of charts the prognosis in 58 tuberculous patients with amyloidosis According to this compilation almost 90 per cent were dead within two years after development of amyloidosis The nature of the underlying tuberculous lesion greatly influences the span of life in the amyloid phase

A review of 30 patients who received treatment for six months to three years for amyloidosis is presented The basic oral therapy consisted of a high protein diet iron and dilute hydrochloric acid Twenty three also received parenteral therapy chiefly liver extract Only four who had arrested tuberculous disease showed definite improvement There was no evidence of improvement in the other cases No sign of anatomic regression of amyloidosis was found in five cases at autopsy

Importance of Symptomless Genital Tuberculosis in Treatment of Sterility H Scherer (Canton Hosp Aarau) found genital tuberculosis during exploratory laparotomy in 12 women seen for treatment of sterility These 12 constituted 10 per cent of all women who sought treatment for sterility In 8 of the 12 women history was completely nonsuspicious of the remaining 4 1 gave history of pleuritis 1 of cervical gland inflammation 1 of peritonitis many years previously and 1 a family history of tuberculosis Five of the women were under 30 and the others under 40 Six patients definitely denied any symptoms referable to the lower abdomen five complained of occasional symptoms during menstruation and occasional abdominal symptoms The remaining patient had had fever for some time Tuberculous salpingitis was present in six tuberculous pyosalpingitis and peritonitis in four and peritonitis and tuberculous endometritis in two

Fresh exudative processes were found in four older chronic productive types in six and completely healed tuberculosis in two Therapy was planned according to this division Mountain cure was advised in six cases and gave excellent results Four women received quartz irradia

(3) S hwe m d W hnsch 4 3 8 359 Ap 8 1944

tion and the two with healed tuberculosis were not treated Examination of the thorax a procedure which should never be omitted in patients with genital tuberculosis revealed no active lung process in any case It is of utmost importance to discover the source of infection in cases of genital tuberculosis preferably in co operation with a municipal tuberculosis organization Cure of such patients is also as important but tuberculous fallopian tubes will always be defective even after complete healing of the tuberculous process and prophylaxis therefore assumes the most important role

[In these cases the pelvic lesions are usually of hematogenous origin from lesions in the lungs and tracheobronchial lymph nodes The clinical diagnosis is aided by the search for lesions of similar origin disseminated in other tissues —Ed]

Harmful Influence of Pregnancy on Advanced Tuberculosis As Modified by Collapse Therapy J W Cutler (Wawa Pa Chest Hosp) describes the immediate and late effects of pregnancy and the responsibilities which follow on advanced tuberculosis in 26 white women who were treated with collapse to control tuberculosis before giving birth to one or more children These women were of about the same social and economic status and were under constant clinical and roentgen observation for varying periods during the past 15 years the average being 9 years They had 48 known pregnancies following collapse therapy and gave birth to 40 children of whom 36 are well Fifteen women gave birth to one child each nine to two children each one to three children and one to four children

Cutler concludes that (1) pregnancy can affect some patients with tuberculosis unfavorably therefore child bearing should be looked on as a potential hazard for a tuberculous mother Exacerbations may occur either in the early months of pregnancy or in the first few months after delivery (2) Collapse therapy has definitely minimized this risk and has restored the right of motherhood to the tuberculous woman (3) If the disease is limited

(4) Am J Obst & G 4 1 19 J 1944

to one lung and the diseased area anatomically well collapsed with all cavities closed the sputum free from tubercle bacilli and the collapse maintained during pregnancy there is little or no risk of reactivating the tuberculosis and one or more pregnancies may safely be undertaken The same is true if there is advanced tuberculosis in both lungs but the disease is controlled with adequate collapse therapy (4) If there is disease in both lungs and the most seriously involved lung is treated with localized collapse the disease in the uncontrolled lung may become active during pregnancy in about 30 per cent of cases This possibility is in itself not a contraindication to pregnancy provided the patient is kept under observation and is willing to accept collapse therapy when first indicated (5) Pneumothorax may be considered an alternative to therapeutic abortion in the presence of active tuberculosis first recognized during the early months of pregnancy When collapse is good and promptly controls the tuberculosis the woman may proceed safely to term (6) Only collapse therapy which produces adequate localized collapse of the diseased portion of the lung such as pneumothorax maintenance oleothorax or thoracoplasty will prevent reactivation of the disease Indirect collapse such as phrenic nerve interruption is not enough Inadequate collapse therapy may be considered equal to no collapse therapy as far as pregnancy is concerned Patients so treated usually do poorly and pregnancy is unadvisable

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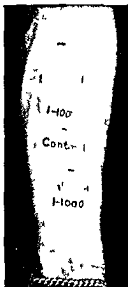
COCCIDIOIDOMYCOSIS ACTINOMYCOSIS

Primary Pulmonary Coccidioidomycosis David M Goldstein (M C A U S) and John B McDonald (M C R) report a follow up study on 75 patients with data on 10 more from a new endemic area in California All of the 75 returned to full duty in three to five months except 6 who were reclassified to continental noncombat duty in eight months One of these had pneumonic con

(5) J A M A 1 4 557 561 Feb 26 1944

solidation with effusion and two verrucous granulomatous skin lesions another had two pulmonic parenchymal cavities The 10 patients appeared to have had a milder infection and all will be returned to duty with a maximum of three months hospitalization

The infection is not difficult to recognize if a history of residence in an endemic region is obtained or a suspected tuberculous patient has negative sputum Thoracic pain is an early and prominent symptom and occurred in 88 per cent of the 85 patients It was always accentuated by cough and deep inspiration was mostly bilateral and persisted after other symptoms had disappeared Cough was present in 88 per cent and was moderately productive in 65 per cent Hemoptysis was present in 18 per cent but had no correlation with severity of the disease or type of pathologic lung condition Chills were present in 66 per cent and fever was a constant finding Sore throat usually slight was noted in 37 per cent Physical signs in the chest were present in only 26 per cent consisting of harsh rough breath sounds rales were infrequent and classic signs of consolidation and effusion were present in several cases Joint pains were present in 28 per cent and were dull and usually localized in the lumbar spine or lower extremities without local swelling or tenderness of the joints



F g 29—P t coc d t t t pt m l t m f d g 48 h s.

Incubation period was 1 to 3 weeks and cutaneous manifestations occurred 8 to 14 days later Erythema nodosum occurred in 19 per cent of the 75 patients and

erythema multiforme in 2 6 per cent while 1 patient had both types A morbilliform rash confined to trunk and *lower extremities was present in 40 per cent of the 10* patients

The coccidioidin skin test is of great value in diagnosis A *negative test* usually excludes the infection whereas a positive test indicates past or present infection In this series coccidioidin as prepared by Smith was used and *0 1 cc of 1 100 and 1 1 000* dilution injected intracutaneously by new tuberculin syringes and small gage needle The control was 0 1 cc of 1 10 dilution of the Bureau of Animal Industry synthetic medium injected similarly Readings were made at 24 48 and 72 hours and results recorded in millimeters of erythema and induration Reactions of 5 mm or more at 48 hours were positive (*Fig* 29) All patients gave positive reactions Only one untoward reaction was noted this patient developed lymphangitis and axillary lymphadenopathy following a strong allergic response Erythema nodosum did not occur in any case as a result of the test

Although there are no typical roentgen findings the more common report on the chest films of the 85 patients stated that the hilar shadows were enlarged on one or both sides associated with increased *bronchovascular* markings extending into the parenchyma of the involved regions Most films showed gradual clearing in the ensuing weeks *Roentgenography* is of paramount *importance in* diagnosis of sequelae Cavity formation occurred in three cases and initial infection was manifested in three other by *primary pleuritic effusion Bronchopneumonic con*solidation of lobar distribution was seen and usually regressed in a few weeks

Symptomatic *conservative treatment is the method of* choice with emphasis on bed rest adequate fluids high caloric high vitamin diet and sedatives Salicylates and iodides *are advantageous for relief of arthralgia* Convalescent blood with high precipitin titer was obtained from two donors and used for transfusion in t ents

critically ill with pulmonary consolidation and effusion In both immediate clinical improvement occurred Sulfonamides appear to be valueless Criteria for discharge were a sedimentation rate of 15 mm or less in 60 minutes and a Weltmann test showing a normal band On admission nearly all patients had an elevated sedimentation rate varying up to 56 mm in 60 minutes when the modified Cutler method with a normal value of 10 mm in 60 minutes was used No death occurred in the 85 patients The two coccidioidal verrucous granulomatous skin lesions in the one patient were removed surgically and the wounds healed without recurrence

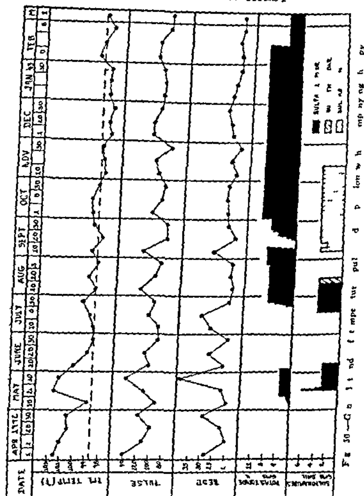
[Michael McLaughlin and Cenac (*United States Naval Medical Bulletin* 43 132 134 July 1944) report the trial of penicillin treatment in one case of coccidioidomycosis without effect —Ed]

Pulmonary Actinomycosis Treatment with Sulfonamides *Nahum R Pillsbury and Joseph D Wassersug* (South Braintree Mass) report a case

Woman 29 with arrested pulmonary tuberculosis was admitted because of pain and swelling in the left chest wall fever and loss of weight of 2 ½ months duration A fluctuant abscess extended from the lower angle of the scapula to the tenth rib A chest roentgenogram showed fluid in the left intrapleural space and fibrosis in the left first intercostal space Sputum and gastric contents were negative for tuberculosis Pus aspirated from the chest abscess showed Actinomyces hominis by smear and culture and later sulfur granules were found in the sputum Potassium iodide medication was begun Abscesses and sinuses began to appear on the left anterior chest wall and the general condition became worse Blood counts revealed anemia and leukocytosis Sulfanilamide therapy was instituted three weeks after beginning of iodide medication During the following weeks she showed gradual clinical improvement (Fig 30) The patient was discharged with all but one sinus healed after 11 months

The impression was that improvement and recovery were definitely enhanced if not actually brought about by sulfonamide therapy A noteworthy point is that the patient who had a proved history of tuberculosis received over 1 800 Gm potassium iodide in seven months without

(6) New E gl d J M d 31 7 74 J 0 1944



evidence of reactivation of tuberculosis In an arrested case of tuberculosis iodine should therefore not be withheld if an indication for its use exists

Actinomycosis of the Chest with Spread to the Abdomen. William E Ladd and Alexander H Bill Jr[7]

(7) New Engl nd J Med. 2 9 48-750 No 11 1943

(Harvard Univ) report a case with successful treatment

Boy 9 had draining sinuses of back and right flank. History revealed six operations for drainage of persistent and spreading abscesses on the posterior chest and in the right flank fever cough and gradual loss of strength and general deterioration He weighed 49 lb had paroxysms of coughing and his back was honeycombed with sinuses interspersed with raw areas of granulation The sinuses contained pus There were rales in the right chest and dulness anteriorly up to the fourth rib There was an apical systolic murmur with precordial thrill The abdomen was distended and shiny with an area of flaccidity and sensory loss below an operative scar in the right upper quadrant The spleen was palpable The hip could not be straightened and there was suggestive clubbing of fingers and toes Blood studies showed red cells 3 400 000 white cells 33 600 with 74 per cent neutrophils 20 per cent lymphocyte 4 per cent monocytes 2 per cent eosinophils nonprotein nitrogen 25 mg and serum protein 7 4 mg per 100 cc Blood Hinton reactions were doubtful once positive once and negative once Tubercle bacilli sulfur granules or fungi could not be demonstrated X ray examination showed cardiac enlargement bilateral pleural effusion and increased lung markings The deepest sinus in the right flank was incised and drained biopsy revealed masses characteristic of actinomycosis

Sulfadiazine 0 4 mg six times daily was given for five days with return of temperature to normal further sulfadiazine administration improved the drainage within two weeks Physical therapy and traction to the right leg resulted in gradual return of motion Sulfadiazine level was maintained between 8 and 12 mg per 100 cc After four weeks he had gained 5 lb After six weeks the back was dry and epithelialized The sulfadiazine dose was cut to 0 5 mg four times daily and blood level remained within the former range After eight weeks he was walking and made ubsequent uneventful recovery Sulfadiazine was continued at 1 5 mg daily for eight months after discharge At last examination there were no cardiac murmur and a clear chest and well healed sinus tracts The spleen was no longer palpable X rays showed the diaphragm on the right still somewhat raised but normal lungs

[There have been various reports indicating the effectiveness of sulfonamides and iodides in actinomycosis including two cases described by Benbow Smith and Grimson (*American Review of Tuberculosis* 49 395-407 May 1944) —Ed]

SARCOIDOSIS

Diagnosis of Boeck's Disease of the Lungs H Mauderli[8] reports a case which illustrates the care and caution to be used when diagnosing Boeck s disease

Woman 34 who had had bronchitis in childhood complained of irritative cough and dyspnea on exertion The roentgenologist gave a diagnosis of cirrhotic possibly nodular tuberculosis possibly Boeck s disease There were no extrathoracic lesions confirming the diagnosis of Boeck s disease Blood picture showed definite shift to the left and eosinophilia sedimentation rate of red blood cells was notably increased Temperature was subfebrile All tuberculin tests were distinctly positive Sputum was not examined Because of the excellent general condition and relative lack of complaints diagnosis of Boeck s sarcoid appeared correct although suspicion of tuberculosis was maintained Later x ray examination during a 2½ month stay in the mountains still justified diagnosis of Boeck s disease because of the stationary finding Prognosis being favorable the patient continued rather strenuous work Films taken at regular intervals showed no change in the condition Therapy included ascorbic acid calcium arsenic and gold injections and quartz lamp irradiation

One and one half year later serious dyspnea developed X ray examination at this time showed considerable change with cavities particularly in the upper lobe of the left lung thus entirely negating the diagnosis of Boeck s disease Tubercle bacilli were found in the sputum Hemoptysis developed and she was sent to a sanatorium The general condition remained satisfactory but tubercle bacilli and elastic fibers were present

Mauderli believes that this case was one of tuberculosis from the very beginning of the disease and that the roentgenograms made previously should have permitted the diagnosis of classic tuberculosis The picture of Boeck s disease of the lung is too indefinite to permit differentiation between Boeck s and tuberculous foci roentgenographically and differentiation is unsafe in view of the importance of early diagnosis and early treatment in tuberculosis

[The pattern of disseminated pulmonary tuberculosis may in some cases bear a close roentgenographic resemblance to that of sarcoidosis The simulation is especially confusing if the tubercu

(8) S hw med Wch h 3 1393 1394 N v 0 1943

is apparently asymptomatic The presumption of tuberculosis should not be dismissed as long as the diagnosis is not otherwise verified Most of these patients should have a period of sanatorium treatment or its equivalent to promote healing while the diagnosis is pending —Ed]

PULMONARY FIBROSIS AND EMPHYSEMA

Acute Diffuse Interstitial Fibrosis of the Lungs Louis Hamman and Arnold R Rich report four cases with autopsy reports presenting a new clinical entity Pathologic peculiarities of the condition are (1) type of inflammation (edema hemorrhage and few leukocytes) which differs from that of ordinary pneumonia produced by pyogenic bacteria (2) enlargement of the lining alveolar epithelial cells (3) necrosis of alveolar and bronchiolar epithelium (4) formation of a hyaline membrane that lines the alveoli (5) marked edema and fibrin deposit in alveolar walls (6) extensive diffuse and progressive interstitial proliferation of fibrous tissue throughout all lobes of both lungs associated with focal organization of intra alveolar hemorrhage (7) presence of eosinophils in interstitial tissue (three of the four cases) (8) absence of stainable bacteria in the lesions These changes cause extreme dyspnea and cyanosis and after only a few weeks to dilatation and hypertrophy of the right ventricle of the heart so that at the end in the one patient who survived the earlier stages of the disease grave symptoms of myocardial insufficiency developed

The clinical picture develops in the following manner Pulmonary inflammation develops insidiously with little local or constitutional disturbance little fever no incapacitation little if any increase in leukocytes Shortly after onset connective tissue begins to proliferate within the alveolar walls and soon dyspnea comes on and grows severe as result of the disturbance of the relation of the capillaries to the alveolar lumen by the interstitial growth of fibrous tissue and gradual compression of alveolar spaces by the rapidly advancing fibrosis Two of the four patients

(9) P H J b H ı k H p 4 177 12 M h 1944

died of slowly progressing suffocation Later circulation in the lungs is impeded pressure in the pulmonary artery is increased and soon the right ventricle becomes dilated and hypertrophied Three of the four patients showed enlargement of the right ventricle Then the symptoms of congestive heart failure appear as more work is done by the right heart death finally occurs from myocardial insufficiency Naturally death is not inevitable after onset The authors have occasionally seen localized forms of the disease in the lungs of patients who recovered but died of other causes these localized forms consisted of small or larger areas of a weblike pulmonary fibrosis similar in appearance to the late stage of this disease The cause of the disease is unknown *No predominating organism has been found in* the sputum no bacteria can be stained in the lesions at autopsy It may be due to an invisible virus but possibility of a chemical irritant must be considered

Emphysema of the Lungs Ronald V Christie[1] (Univ of London) uses the term emphysema to mean chronic vesicular or hypertrophic emphysema of the lungs acute senile and localized emphysema probably being distinct entities The emphysematous lung is deformed in at least three ways (1) Many lobules or air sacs are misshapen and the alveolar ducts are dilated so that air is no longer thrown into the atrium as a jet (2) Septums between alveoli may disappear so that the supporting framework of the air sac may be lost The sacs or bullae then become comparable to bags of tissue paper which are easily compressed and easily dilated (3) The amount of air in the lungs is usually increased but not proportionately to the severity of the disease nor is the volume of the emphysematous lung at rest ever as great as the volume of a normal lung in full inspiration Thus the lung as a whole in emphysema is not overstretched or overdistended any more than a normal lung is overdistended or overstretched when a breath of moderate depth is taken Changes in the medium and larger bronchial lumens are variable but the

(1) B r M J 1 105 108 Jan 2 143 146 Jan 29 1944

terminal bronchioles and alveolar ducts are usually dilated sometimes extending to the smaller bronchi thus producing a picture resembling cylindric bronchiectasis

Recent investigations suggest that elasticity of the lung may be entirely lost at a comparatively early stage of emphysema not as is usually assumed secondary to over distention because there is none in the emphysematous

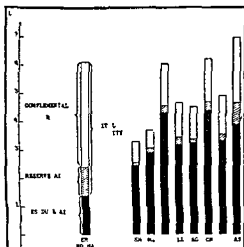


Fig 31—L ng v l m d t bd mphy m C f m l ft
to ght d f ty f dy p

lung Rather this loss of elasticity could be the direct cause of expansion of the thoracic cage Changes in pulmonary circulation consist of torn and obliterated capillaries and widespread atherosclerosis The pulmonary vascular bed is diminished and the work of the right ventricle may be increased although total blood flow through the lung is not diminished at least not until heart failure supervenes Peripheral lymphatics may show cellular infiltration and the characteristic pigmentation of the lung probably reflects deficient lymphatic drainage

Grossly the lesions appear most pronounced on the sur

face of the lungs especially along the margins Microscopically they extend throughout the lungs although dilatation of air sacs is most conspicuous at the periphery The most important disturbance of function is inability to ventilate the blood usually apparent many years before death Deficient ventilation is measured by analyzing the arterial blood (see Table) In severe cases there is gro

ARTERIAL BLOOD IN MODERATE SEVERE AND FATAL EMPHYSEMA

Case	Oxygen			Carbon Dioxide				Comment
	Capacity	Content	Saturation	Content (Whole Blood)	Content (Plasma)	pCO_2 (calculated)	Alveolar pCO_2	
	Vol %	Vols %	%	Vols %	Vol %	mm. Hg	mm. Hg	
1	19.4	17.5	90	51.4	6 6	47	39.3	
						43	38.5	
	21.0	19.4	9	47.2		44	45.4	
2	6 4	21.6	8	53.1		83	71	Satu t on 10 % when b th ng 100% o ygen
	28.6	2 4	78	51.1		73	68	
3					101.7	93		Venous blood th out tas s
	20.9	15.1	72	74.5	88	90, 84, 91		After ve sect 900 cc
				74.1				

deficiency in both oxygen absorption and carbon dioxide elimination in milder cases this deficiency is manifest only when demands of metabolism are increased by exercise The defect appears to lie in deficient ventilation of alveoli rather than in any barrier between alveolar air and blood

Dyspnea in emphysema is caused by stimulation of the respiratory center by carbon dioxide retained in the blood gaseous acidosis occurs and dyspnea results Without bronchospasm there is no orthopnea because there is no pulmonary congestion

Diagnosis is difficult because many signs are misleading or unreliable Diagnosis should only be considered certain when dyspnea on exertion of insidious onset not due to

bronchospasm or left ventricular failure appears in a patient with some of the physical signs of emphysema and chronic bronchitis or asthma absence of dyspnea or of physical signs casts doubt on the diagnosis but does not exclude it The vital capacity test is of value because it usually shows decrease from normal Determination of loss of elastic recoil is valuable but not completely reliable

Treatment is symptomatic as elastic tissue cannot regenerate and nothing can restore the lung structure Ephedrine to relieve dyspnea deflation of the lung to increase efficiency of respiration respiratory exercises to deflate the lung and to increase use of the diaphragm are among the methods used When heart failure supervenes oxygen is given Although recovery from heart failure in emphysema is uncommon Christie had a patient who recovered from two attacks after being moribund In the first oxygen was given continuously for a week in the second for 10 days He died during a third attack and diagnosis was confirmed at autopsy

[See the article by Darling *et al* this YEAR BOOK p 149—Ed]

NEOPLASMS

Gynecomastia and Pulmonary Carcinoma In 1941 E B del Castillo F A de la Balze and J Reforzo Membrives reported three cases by gynecomastia occurring in the course of bronchopulmonary carcinoma these patients also showed hypertrophic osteo arthropathy They now report another case

In a man 63 pain and swelling developed in the right knee three years previously and progressed slowly later the same symptoms developed in the ankles shoulders and wrists For a year the hands and feet had been increasing in size with enlargement at the end of the fingers The breasts increased for two years with sensitiveness of the nipples and areolar region Body weight decreased 14 kg in 2½ years Sexual function was retained until onset of this illness then marked decline in libido occurred

The skin of the face and upper and lower extremities was pigmented and numerou melanotic nevi were distributed

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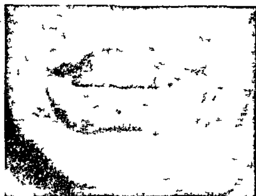
over the body The nails on both hands and feet were thick ened opaque striated and convex in both diameters Genital hair was sparse and the mons veneris had a feminine con formation Subcutaneous tissue in the hands and feet was com pact and adherent to deep planes The patient appeared malnourished Articular movements were difficult and caused pain this was true al o in the vertebral column which dis played marked kyphosis Size of the hands was increased principally in the radiocarpal cubitocarpal joints and at the ends of the fingers Similar but more marked changes were present in the feet The skin of both areolas was pigmented and both mammary zones were diffusely swollen to the size of a small orange the nipples were large erect and of red dish hue Mammary palpation was difficult because of tender ness Physical and roentgen examination revealed broncho-pulmonary epithelioma

Sedimentation rate was increased Blood count showed 4 100 000 red cells 80 per cent hemoglobin and 10,300 leuko cytes with 81 per cent neutrophils 11 per cent lymphocytes and 8 per cent monocytes The only abnormal finding on urinalysis was increased urobilin Serologic tests were nega tive Neoplastic cells were present in the sputum Excess estrogenic hormones were present in the urine Androgens were present in normal quantity

These factors suggest the possibility that the pulmonary tumor secretes a substance of feminizing influence or that the tumor exercises an influence on some endocrine gland The breast is a secondary sex character and hence pro duced by two factors (1) a chromosomic factor constitut ing capacity of the organ or tissue to respond and (2) a general factor represented by hormonal influences In pathogenesis of most gynecomastias and especially those appearing with bronchopulmonary epitheliomas there are both predisposing and precipitating factors

Predisposition to mammary enlargement is congenital and consists of an intersexual condition in the chromo-somes In most patients this is the only manifestation but in the case reported there were also loss of libido and feminine hair distribution The patient s history also re vealed that there had been some mammary enlargement at puberty which gradually disappeared The precipitating pathologic mechanism is an increa e in quantity of estro

and multiple adenoma Sufficient attention to the soft murmur and *knowledge of Rodes report would have aided diagnosis*



Fg 32—M lt pl m ll h m g m f l l p



Fg 33—T m

Exploration of the right che t va decided on because the hadows were larger Two hemangiomas one on the posterior *margin of the lower lobe and one about half as large on the*

from recurrence his disability is negligible and often absent A small proportion may be left with a discharging sinus but with modern methods this should not happen often Most of the survivors in Brock s series were able to return to work which often included manual labor for long hours Even in such patients who succumb to recurrence the operation is worth while since by removal of the obstructed and infected lobe or lung the toxemia fever and sputum disappear and they are able to carry on normally almost to the end

[Interest continues in the incidence of bronchial carcinoma and its possible increase Steiner (*Archives of Pathology* 37 185 195 March 1944) studied this question at the University of Chicago and found no evidence of a real increase in the disease In 5 515 necropsies the percentage revealing bronchial carcinoma was 2.3 This neoplasm represented 7 6 per cent of all malignant tumors and 10.3 per cent of all carcinomas Johnson and Reinhart (*Ohio State Medical Journal* 39 1017 1018 November 1943) studied the autopsy material from the Department of Pathology Ohio State University and found a progressive increase in all carcinomas over a 25 year period but no absolute increase in carcinoma of the lung —Ed]

Multiple Cavernous Hemangiomas of Lungs Successfully Treated by Local Resection of Tumors Robert M Jane (Univ of Toronto) reports a case in which the largest tumor was the size of a hen s egg

Man 30 after strenuous exertion a year previously coughed up bright red blood More serious bleeding occurred later Chest films at that time were negative and there were no tubercle bacilli in the sputum He remained well for a year One month before admission he coughed up blood three times in one week and lost weight There were cyanosis of lips and finger nails and multiple small hemangiomas on the lower lip (Fig 32) said to have been there a long time There was no other abnormality except a soft blowing murmur in the region of the right cardiophrenic angle There was no cough fever or sputum Bronchoscopy revealed no blood or suggestion as to source of bleeding White cell count was 11 400 with 78 per cent neutrophils 20 per cent lymphocytes 2 per cent eosinophils Shape of red cells was normal There were marked microcytosis and hypochromia Sedimentation rate was 8 *Tuberculin test was negative Chest films* showed two shadows in the right lung and one or possibly two in the left (Fig 33) Diagnosis lay between multiple hemangiomas

(4) Brit J Surg 31 0 J y 1944

was closed and the lung re expanded by suction applied to an intercostal tube drain Recovery was uneventful (Fig 35)

The specimen was a globular cystic mass containing thin milky fluid. The wall was thin and vascular Two thickened areas appeared to contain cartilage and another appeared to be muscular (Fig 36) Microscopically the cyst was lined with respiratory epithelium which for the most part was lying on a fibrous tissue base In some areas there was no epithelial lining In the aforementioned areas however car



F g 34—Upp med t l p t p j t g tow d right de

tilage and *considerable smooth muscle tissue* were found In other regions were numerous mucous glands nerves and blood vessels Final diagnosis was bronchiogenic cyst of the superior mediastinum—reduplication cyst of the respiratory tract

The mode of development of this anomaly is probably similar to that of congenital cysts of the lung Most cysts in the mediastinum unlike most intrapulmonary cysts have no connection with the air passages Chiari reported five cases of diverticula of the trachea all of which were located on the right side just above the carina It is possible

margin of the middle lobe were seen at once and resected locally Pleura over the base of the larger lesion was incised and four vessels each 5–6 cm in diameter were isolated ligated with fine silk and divided. Blood supply to the tumor being controlled the growth was dissected from the surrounding lung tissue The excavation in the lung was obliterated and oversewn with chromicized catgut Blood supply of the smaller tumor was controlled by passing a wedged intestinal needle deep into it and doing mass ligation the tumor was then removed Recovery was uneventful He felt well was working and capable of much more exertion than formerly Cyanosis was distinctly less

Nine months later the left chest was opened disclosing a hemangioma on the costal surface near the posterior rounded border of the lower lobe and another on the lower border of the lobe more anteriorly Each tumor was resected over forceps and the defect in the lung closed with a running cat gut suture This was followed by further improvement in health and increase in exercise tolerance

Local resection appears to be preferable unless the tu mors are so massive as to require lobectomy or pneumonec tomy Because of danger of fatal hemorrhage operation should not be delayed

Bronchiogenic Cysts of the Mediastinum Three surgi cally treated cases are reported by W E Adams and T F Thornton (Univ of Chicago) one of which is presented here

Man 32 complained of dizziness and weakness for a year Physical examination was essentially negative An x ray of the chest revealed in the superior mediastinum a round opaque area projecting to the right of the mediastinum just above the level of the aortic arch (Fig 34) On fluoro copy this shadow was found just in front of the vertebrae and moved upward when the patient swallowed This differentiated the lesion from a ganglioneuroma or neurofibroma An operation was performed by approach through the bed of the fifth rib after a long section of it was removed When the lung was retracted downward a thin walled grayish cyst about 2 in in diameter was seen lying close to the trachea and esoph agus The cyst was dissected free from the surrounding structures down to the trachealis mu cle to which it was densely adherent and from which it appeared to be arising It was removed without entering the trachea the chest wound

(5) J Tho ci S g 12 503 516 Augu t 1943

origin Bronchoscopic examinati m i m licated in the presence of infection and symptoms of pre sure

Because of the rarity of thi le ien and difficulty in differential diagnosis exploratic n i mdicated Even when the cysts are asymptomatic urgery i adv i able because

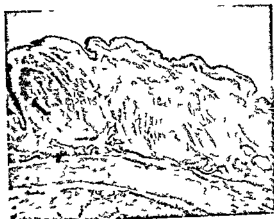


Fig 36—Cy t w ll a wh m h mooth m l w p nt l g p tl l m b d l t col m a

of likelihood of their increasing in size or becoming infected Drainage of the cy t is to be avoided because a persistent inus may result When complete excision seemed hazardous partial excision with destruction of the lining mucosa of the remaining part gave good results in two cases When the cyst is already infected two stage drainage with subsequent excision is suitable

Intrathoracic Neurogenic Tumors Edward M Kent Brian Blades Anibal Roberto Valle and Evarts A Graham (Washington Univ) report 18 cases of proved intrathoracic nerve tumor and 3 others of probable but not proved neurogenic tumor with an analysis of 105 cases from the literature Of the 21 cases tumors were in the posterior part of the thorax in 19 and in the anterior

( ) J Th S g 13 116 161 Ap 1 1944

that such a projection might be pinched off during the stage of development giving rise to formation of a cyst similar to that in the case described

Clinical course depends on size and location of the cyst and whether pressure symptoms on adjacent structures

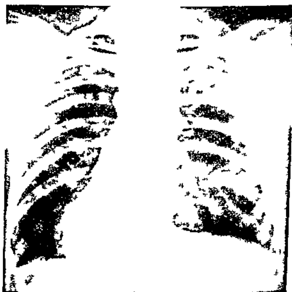


Fig 35—El days aft o al of y t fifth r b m ng

are present Many cysts produce no symptoms and are found accidentally on x ray or fluoroscopy of the chest Thirteen of 25 cases collected by Heuer and Andrus were first discovered at autopsy Pressure on the trachea or large bronchi may produce symptoms of anoxia or lead to chronic infection of the respiratory passages Occasionally the cyst becomes infected as in one of the authors cases and gives rise to pulmonary suppuration Diagnosis is difficult but is aided by x ray and fluoroscopic examination Location in the region of the trachea or major bronchi with vertical movement on swallowing tends to differentiate it from dermoid cysts and tumors of nerve tissue

ever such extensive surgery is contraindicated at one stage the intraspinal portion should be the point of attack

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TRAUMA

Experiences with Chest Wounds from the Pacific Combat Area. Emile Holman (M C U S N R) reports that of 36 patients with gunshot wounds of the chest seen at Mare Island Naval Hospital 20 showed marked dyspnea and 16 hemoptysis usually mild 19 hemothorax with 12 aspirated 27 times 3 aspiration accompanied by replacement with air 2 complicated by empyema 7 hemothorax not aspirated and followed by uncomplicated recovery 8 retained foreign bodies removed in 5 8 fractured ribs for which no particular treatment was necessary 6 sucking wounds requiring early closure 6 complicated by empyema 2 of whom will require thoracoplasty for cure There were no deaths in these patients evacuated to the mainland from the South Pacific area

Certain principles should be recognized and followed in treatment of thoracic injuries The immediate care of wounds of entrance and exit often determines the final outcome Bullet wounds are frequently small appear perfectly clean heal like surgical incisions and after a month defy detection For such sharply cut wounds a simple dressing is sufficient Bullets shrapnel and mortar fragments may produce ragged dirty looking wounds with severely traumatized edges capable of acting as excellent culture mediums for growth of organisms Such wounds if seen in 6–10 hours should be excised under local anesthesia the raw surfaces smeared with a sulfonamide mixture of sulfathiazole and sulfanilamide equal parts and the skin edges loosely approximated Sulfathiazole or sulfadiazine 4 Gm is given by mouth immediately followed by 1 Gm every four hours for three to five days If seen later than 10 hours after injury without obvious infection a cleansing debridement is performed and if there is no sucking

(7) A S g 119 1 5 J 1944

mediastinum in only 2 The group from the literature also contained only two with tumors in the anterior mediastinum

The essential characteristics of nerve tumors in the thorax do not differ from those of peripheral nerve tumors elsewhere The symptoms may be unimportant or more severe and of the type resulting from involvement of certain nerves In many cases the tumor is discovered by x ray examination made for other reasons Sometimes patients complain of pain which is radicular or referred along an intercostal nerve Other symptoms sometimes present are dyspnea stridor unproductive cough hoarseness with paralysis of a vocal cord and Horner s syndrome from involvement of the sympathetic chain The tumors present a rather definite roentgen picture They are usually single within the thorax and since most of them are adjacent to or within the posterior superior mediastinum they present a sharply circumscribed nonpulsating round mass in the posterior upper thorax. In some cases there is an associated erosion of the ribs adjacent to the mass A lobulated appearance is always suggestive of rapid growth and therefore of malignancy Otherwise there are no characteristic x ray findings which justify diagnosis of malignancy unless metastases can be demonstrated Even demonstration of a pleural effusion does not justify an assumption of malignancy A diagnostic test dose of radiation is of little or no value in establishing malignancy because neurogenic tumors even malignant ones are little affected The only effective treatment for intrathoracic nerve tumors is surgical removal Because of the high incidence of malignant change it is wise to remove these tumors as soon as diagnosis is made unless removal is contraindicated for other reasons. The operative approach is planned according to position of the tumor Since most tumors are in the posterior mediastinum a posterior approach is most often used If the patient has an hour glass tumor both intraspinal and intrathoracic parts should be removed at the same operation. If how

raw surfaces thus produced may be skin grafted immediately or covered with vaseline gauze or sterile cellophane A firm voluminous dressing well strapped in place by adhesive plaster encircling the chest should be applied and not changed for 7–10 days in ab ence of contraindications *Sutures approximating contaminated muscle and* subcutaneous tissue must be gently applied and loosely tied to avoid excessive strangulation and pressure necrosis of included tissues Necrotic tissue serves as culture medium for bacteria and is frequently responsible for breaking down of sutured wounds When muscles are absent at the site of defect in the thoracic wall re ection of one or two ribs on one or both ides of the defect will permit closure of the now more mobile soft parts

Liberal use of sulfonamides locally and orally is indicated in all cases The mere presence of hemothorax warrants neither operation nor aspiration Aspiration may be limited to patients with respiratory embarrassment or complicating infection or if blood or fluid is not reabsorbed after two or three week If dyspnea recurs promptly after simple aspiration relief may be attempted by aspiration and replacement with air A hemothorax or serosanguineous effusion that persi t beyond two or three weeks without diminution may be a pirated but replacement with air at this date is unnecessary Removal of foreign bodies in the chest may generally be postponed until ideal conditions prevail as for fluoro copy and proper anesthesia Small symptomless foreign bodies may be retained without harm Linear wounds produced by debridement or *air at this date is unnecessary Removal of foreign bodies* may be closed with deeply placed right angled lock stitch sutures of catgut on atraumatic needles Leakage of air as demonstrated by dripping water over the line of suture *must be controlled by the insertion of adequate re enforcing* sutures

Incisions in the myocardium may be closed with interrupted silk or cotton sutures Following operations on the heart the pericardium should be closed loosely with

wound the tissues are not sutured the raw surface being treated with sulfonamides and a dressing of vaseline gauze Failure to excise traumatized tissue in the wound of entrance may lead to localized infection and subsequent extension to hemothorax resulting in massive empyema Large sucking wounds require immediate debridement and closure of the opening if possible When first seen on the battlefield such a wound after application of a sulfonamide may be closed with massive dressings or a sterile glove over the opening and a tight adhesive bandage encircling the chest At first opportunity such wounds must undergo cleansing debridement and removal of fragmented ribs foreign bodies and blood clots in the chest cavity Sulfonamides are applied to all exposed pleural surfaces and the defect in the thoracic wall is loosely closed With gross contamination of the pleural cavity a mushroom catheter is placed in the first intact intercostal space below the wound and closed with a clamp until underwater drainage is established at the bedside Considerable ingenuity may be necessary to close the defects in the thoracic wall depending on location and size Defects in the lower chest e g below the level of the dome of the diaphragm may be closed by stitching the diaphragm to the parietal pleura at the upper border of the defect the diaphragm having previously been paralyzed by transpleural crushing of the phrenic nerve as it courses over the pericardium

Muscles of the thoracic wall (pectoral latissimus dorsi and trapezius) should when possible be approximated by overlapping thus providing two lines of suture Relaxing semilunar incision in the muscle well away from the defect may be made on one or both sides depending on the ease with which the muscles are approximated There should be sufficient relaxation of the muscle to permit some overlapping and approximation without tension If no muscle is available subcutaneous fat and fibrous tissue may serve as one layer and skin as the second When skin alone is available semilunar relaxing incisions may be necessary on one or both sides to effect closure without tension The

raw surfaces thus produced may be skin grafted immediately or covered with vaseline gauze or sterile cellophane A firm voluminous dressing well strapped in place by adhesive plaster encircling the chest should be applied and not changed for 7–10 days in absence of contraindications Sutures approximating contaminated muscle and subcutaneous tissue must be gently applied and loosely tied to avoid excessive strangulation and pressure necrosis of included tissues Necrotic tissue serves as culture medium for bacteria and is frequently responsible for breaking down of sutured wounds When muscles are absent at the site of defect in the thoracic wall resection of one or two ribs on one or both sides of the defect will permit closure of the now more mobile soft parts

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Incisions in the myocardium may be closed with interrupted silk or cotton sutures Following operations on the heart the pericardium should be closed loosely with

widely spaced interrupted sutures to permit escape of blood or fluid that might produce cardiac tamponade

Exploratory thoracotomy can usually be done through intercostal incisions without rib division or excision if a suitable self retaining rib spreader is available When done for removal of foreign bodies every effort must be made to avoid or limit division of adhesions between visceral and parietal pleurae to avoid unnecessary pulmonary collapse Empyema developing the first two or three weeks after injury should be drained by air tight catheter rather than by resection of rib or intercostal incision Re expansion of collapsed lung is accelerated by forced expiratory exercises The patient inspires deeply and then forcibly expires against a closed nose and closed mouth With an empyema cavity or pneumothorax the patient is required to do the forced expiratory exercises as often as every hour during the day They must not be used with an open bronchial fistula

After traumatic lesions of the chest involving lacerations of the lung prolonged convalescence is necessary Return to duty should be postponed until roentgen evidence of intrapulmonary damage has largely disappeared and is minimal

Findings in 262 Fatal Accidents are discussed by G R Osborn (Derby) As in the brain injuries due to direct violence and to contrecoup also occur in the lungs and heart with a third type due to pincer forces in V shaped spaces The heart shows a fourth type of lesion which is dependent on its rhythmic contraction The thorax is typically compressed from the front and sides the posterior parts near the spine being relatively fixed hence the typical contrecoup lesion is posterior

Lung lesions from direct violence are rib markings well seen in infants and animals Lung lesions from contrecoup may be seen in all stages of development The earliest stage is a hemorrhagic straight line on the lung in an almost constant position corresponding to the angle

(8) Lancet 2 7 284 Sept 4 1943

of the ribs A row of blisters can often be seen in addition to the subpleural blood mark The hemorrhagic line is produced by varying combinations of subpleural hemorrhage and hemorrhagic concussion of the underlying alveoli A common extension of this posterior contusion is to the upper part of the lung in the cupula pleurae The further stage shows extension laterally and anteriorly The lateral extension may become confluent with phrenicocostal contusion and rib markings If the lung absorbs the force of the incoming ribs as in infants and animals the near lung



Fig 37—In bl t j et l e l t ffed w th ed blood cell wh h mp l eol cap ll ri outline of latt e ly seen beca se f cr wding f l comp b cur tea through wh h ed cells ha escaped In h m rrh g d m p ll ri so d l ted th t th outl bscu ed d d blood lls ly se n po g to l l s. Left l l bl t ght l l ct t p lmo ry dema.

may protect the more distant one if the alveoli transmit the force as in adults with protective reflexes developed the nearer lung may show less damage

V shaped spaces are weak spots in the thorax since pincer forces may be applied to the sides these contuse the limbs of the pincers or the structures in the V spaces The simplest example is the phrenicocostal contusion The posterior part of the right middle lobe is apt to be nipped between upper and lower lobe The anterior margin of the lungs is an apparent exception to the danger of the V space

The commonest accident in the present series was a fall (in the street at work from moving vehicles and down various distances) The greater the force the higher the

probability of visceral lesions They are the rule in truck bus and airplane injuries and in bombings especially in persons in confined spaces

Acute pulmonary edema occurs mostly in conditions associated with shock It is only the most dramatic manifestation of peripheral circulatory failure Histologic changes of acute pulmonary edema are essentially those of shock arteriolar spasm with dilatation of the capillaries and venules resulting in stasis and edema The morbid anatomy of pulmonary contusion may become confused by the addition of acute hemorrhagic edema Microscopic differentiation however is easy (Fig 37)

Pulmonary embolism caused about 5 per cent of death in patients without head injuries It was not found in patients with head injuries probably owing to restlessness of such patients Pulmonary edema occurred in 24 per cent With four exceptions the accidents caused little or no blood loss This indicates that blood loss protects against acute pulmonary edema and that transfusions which raise the blood volume above its original level may precipitate acute pulmonary edema

Chest Injuries and Traumatic Asphyxia J M Stickney and A P Hagedorn report a case

Man 54 was found unconscious under an overturned tractor The steering wheel rested on the right side of his chest and abdomen On admission his appearance was remarkable There was marked cyanosis from the clavicular and deltoid region up including the entire neck face and head Trunk and extremities had normal color There were multiple petechial hemorrhages over the entire distribution of cyanosis petechiae in the buccal mucosa and extensive subconjunctival hemorrhage Respiratory distress was suggestive of an attempt at forced expiration with marked distention of the veins of the neck The mouth was filled with tobacco adding to difficulty of respiration but this was easily aspirated to free the airway There was no tracheal obstruction Hands were clenched arm flexed and legs sometimes flexed and sometimes extended sometimes flaccid and sometimes spastic and the head was thrown back to give the appearance of decerebrate rigidity There was slight subcutaneous emphysema in

(9) Proc Staff Meet Mayo Clin 19 207 213 Apr 19 1944

the right upper anterior axillary line A roentgenogram of the thorax revealed many fractured ribs on the right side in the posterior axillary line and a small amount of fluid in the right pleural space There was no evidence of extensive emphysema. Pulse rate was 80 respiratory rate 22 blood pressure 138/98 and rectal temperature 100 F There was no sign of shock

Oxygen 100 per cent was given with mild sedation Lumbar puncture three hours later gave essentially negative results and showed spinal fluid under normal pressure The patient remained in coma for 18 hours and then gradually returned to normal At all times after the first hour blood pressure remained at about 130 70 Examination of the fundi revealed a small hemorrhage in the superior nasal portion of the right retina Eight days after admission he was allowed out of bed Four days later he first noted diplopia when looking at a distant object this changed to diplopia at closer range especially when looking to the right Neurologic examination gave negative results except for weakness of the external rectus muscle of the right eye Roentgenogram of the head revealed no abnormality Since discharge he has improved in every respect except for weakness of the external rectus muscle of the right eye

Mass Asphyxia Medical Aspects of the Tube Shelter Disaster Keith Simpson (Guy s Hosp) presents autopsy findings in four selected cases of the disaster in which 173 persons died He discusses the mode of death in these cases as compared with asphyxial events in general and particularly as encountered in criminal deaths from asphyxia

An emotional person may die of anticipating asphyxia in a matter of seconds only sufficient for a mere fluttering arrhythmia collapse and death Pressure on the neck particularly on the carotid sinus may induce a classic vasovagal inhibition a reflex arrest of respiration and circulation A girl of 4 (Case 1) had a local bruise on the left side of the neck over the larynx and booted foot abrasions crushed down from the chin across the neck which was violently hyperextended Inhalation of vomitus with impaction of food at the glottis may cause reflex vagal inhibition and rapid death A boy 7 and girl 2½ (Cases 2

(1) I t 2 309 311 S pt 11 1943

and 3) inhaled vomit and this may have caused death without prolonged asphyxia Local biochemical changes in the heart muscle ensue with great rapidity in asphyxia, and their effects on its contractility and conductivity are most significant in relation to death More general changes in blood chemistry also appear with alarming rapidity in asphyxia An even more important result of oxygen starvation is seen in the brain and spinal cord tissues The time required for disappearance of electric potentials after the beginning of cerebral anoxia varies between 10 seconds and 2 minutes

Crushing pressure on the chest especially if involving the heart as was evident in Cases 1 and 3 so much more likely in a young subject with an elastic compressible thoracic cage may produce arrest of respiratory and circulatory rhythm A boy of 18 (Case 4) showed grave thoracic and abdominal crushing but survived long enough to show equally serious secondary changes resulting from these injuries namely traumatic paralytic dilatation of the stomach and small intestine Increasing compression of the neck may produce congestion in the head above this level with small hemorrhages occurring in showers in the skin brain and meninges Their effect on the bulbar centers is similar to that of contusional edema with resulting embarrassment or failure of respiration Such hemorrhages were noted in Case 4

Three Cases of Poisoning by Irrespirable Gases (Phosgene from Trichlorethylene, Nitrogen Dioxide Carbon Dioxide with Reduction of Oxygen) are reported by E H Derrick and D W Johnson (Brisbane)

CASE 1 —Man 26 employed as dry cleaner and exposed to trichlorethylene left the plant in apparent good health One and a half hour later he collapsed and died Autopsy revealed intense edema of the lungs there was no inflammatory reaction The delayed action severe pulmonary edema and sudden fatal collapse are consistent with phosgene poisoning whereas workers poisoned by trichlorethylene become drowsy or unconscious during exposure Trichlorethylene decomposes in high temperatures It was assumed that the man who had been

(2) M J Au t alia 355 358 O t 30 1943

smoking in the poorly ventilated cleaning room by inhaling trichlorethylene through lighted cigarets had caused its decomposition with phosgene formation

CASE 2—Youth 19 had lighted a fuse attached to a gelignite cartridge in a deep well He came to the surface apparently unharmed and worked for the rest of the afternoon. At 5 00 p m he complained of headache At 10 00 p m. he began vomiting became dyspneic and died the next morning at 8 30 Autopsy revealed an acute inflammatory reaction in the upper respiratory tract and edema of the lungs Microscopic examination showed acute inflammation of the terminal bronchi and bronchioles widespread rupture of the alveoli extravasation of lymph and infiltration with polymorphonuclear leukocytes Investigation revealed that the gelignite cartridges ⅞ in in diameter were placed in holes 2 in in diameter There was an excess of air around the charge leading to excessive formation of nitrous fumes consisting of a mixture of nitric oxide the dioxide and its polymer both latter gases being toxic. In addition carbon monoxide is formed

CASE 3—Man 26 went into a vat which had been used for storing fermented malt at 8 45 a m At 10 00 a m. he was found dead at the bottom of the vat Autopsy revealed death from asphyxiation Fermentation of sugar to alcohol and acetous fermentation were probably going on at the same time in the vat both unsuitable for respiration The first produces carbon dioxide and the second abstracts oxygen

Case 1 illustrates an important industrial hazard for trichorethylene is used extensively in cleaning metal parts and clothes Nitrogen dioxide is important in military practice when bombs and shells explode in confined spaces and is a risk to civilians handling explosives The combination of carbon dioxide and reduction of oxygen is known to miners as black damp

[See Camiel and Berkan this YEAR BOOK p 185—Ed]

Pulmonary Edema The vast expansion of industrial production has exposed a greatly increased number of workers to the hazards of toxic fumes with a resulting rise in incidence of pulmonary edema Toxic agents implicated are chiefly oxides of nitrogen phosphorus oxychloride phosphorus pentachloride phosphorus trichloride methyl bromide chlorine cadmium and dust from certain alkaloids J M Carlisle (Rahway N J) describes a

(3) J A M A 1 3 947 948 D 11 1943

simple method proved effective in prevention as well as treatment of pulmonary edema following exposure to toxic gases

METHOD—This consists in absolute bed rest and immediate administration of 100 per cent oxygen under atmospheric pressure The expiratory valve of the efferent tube leading into the water bottle is set to afford 1 cm water pressure This pressure is gradually though fairly rapidly (5–10 minutes) raised to not more than 6 cm water pressure Oxygen administration is continued for one to three hours depending on the patient s condition Trial periods are made of breathing without the mask for 10–15 minutes and if any breathing difficulty cyanosis or coughing is observed the mask is reapplied

With this method no fatality from pulmonary edema has been observed in nine years In some instances considerable time may elapse between exposure and delivery to the hospital In most of these advanced cases in which actual pulmonary edema is present a 1 100 solution of epinephrine is given by the oral nebulizer prior to or during administration of oxygen This is also a valuable adjunct when the irritant has produced bronchiolar spasm obstructing the intake of oxygen Epinephrine may be given intermittently or continuously by applying the nebulizer to a side arm of the oxygen tube Carlisle advises against use of oxygen carbon dioxide mixtures a mixture of oxygen and helium has proved beneficial in a few case

The oxides of nitrogen represent in many industries the commonest cause of pulmonary edema Since the reaction often has insidious onset every industrial physician should be on the alert for its early detection

Treatment of Pulmonary Edema Due to Gas Poisoning in War and Civilian Life Alvan L Barach (Columbia Univ) states that inhalation of oxygen and helium oxygen mixtures under positive pressure is valuable in treatment of obstructive dyspnea and acute pulmonary edema the *only contraindication* is presence of shock Experience with use of positive pressure respiration in cases of industrial gas poisoning indicates that edema of lungs may be pre

(4) New Engl J Med 230 216 3 Feb 4

vented if edema has already occurred it responds to this treatment better than to any other. A pressure of 3–6 cm water is usually effective in treatment of pulmonary edema. If all signs of edema have cleared, gradual reduction of pressure over some hours is best. Prevention of pulmonary edema after exposure to an irritant gas is advocated by inhalation of air or oxygen against positive pressure for two or three hours and then institution of trial periods of freedom from positive pressure to determine whether or not edema is developing. Since it may develop as late as 12 hours after exposure, means for providing positive pressure should be at hand in any case in which contact with a poisonous gas is known to have occurred.

Inhalation of a spray containing 0.5 cc of 1 per cent epinephrine is helpful in cases with bronchial spasm. Inhalation of 0.5–1 cc of 1 per cent neo-synephrin increases the lumen of the tracheobronchial tree by vasoconstriction.

In civilian disasters in which phosgene or other gases are liberated, immediate administration of positive pressure is advocated. Although inhalation of oxygen enriched air overcomes the arterial anoxia, prolongs life and in some cases saves it, in many cases discharge of serum continues with impairment of bronchial drainage, secondary infection and bronchopneumonia. The sulfonamides are useful to prevent infection, but the primary pathologic condition is that of hemorrhagic inflammatory edema, with infection only secondarily produced as result of bronchial obstruction. Use of positive pressure is more valuable than rest, warmth, oxygen and sulfonamide administration, for it prevents pulmonary edema, the consequences of bronchial obstruction and bronchopneumonia.

Administration of positive pressure of 6 cm may be sufficient to heal edema in one to three hours. Pressure may be begun at 3, 4, 5 or 6 cm, depending on co-operation of the patient. If pulmonary edema disappears during application of positive pressure of 3–6 cm for several hours, pressure should be lowered to 2 cm for one to two hours more, lowered further to 1 cm for one or two hours

and then stopped If pulmonary edema has cleared trials are made of breathing without the mask for 5–30 minutes, and if coughing and edema do not supervene treatment is discontinued If coughing and edema recur the mask is reapplied and positive pressure used as long as required. When pressure is applied by the hood lower pressures are used since positive pressure is then exerted on the pulmonary capillaries in both inspiration and expiration. Pressure of 3 cm water is effective in terminating clinical pulmonary edema although 4–5 cm may be used in severe cases

If gas poisoning occurs in combat areas or in localities where oxygen in cylinders is not immediately available the metered positive pressure mask may be used by detaching the collecting bag and rubber tube Then the patient inspires through the inspiratory valve that connects with the outside air during expiration the inspiratory valve closes and the expired air passes out through a constricted orifice representing a pressure of 2–10 cm water A three hour period of breathing against positive pressure is recommended followed by gradual lowering of pressure to that of the atmosphere for one to three hours longer depending on estimation of severity of exposure If the metered mask is used with air the inner surface of the mask should be equipped with an additional emergency inspiratory valve so that a plentiful inlet of air will occur without negative pressure developing within the mask Air containing 40–70 per cent oxygen is better than 100 per cent oxygen under positive pressure Without a mask the patient should be instructed to exhale through partially closed glottis thus increasing intrapulmonary pressure during expiration

[For a description of Barach s oxygen meter mask see the 1943 YEAR BOOK OF GENERAL MEDICINE, pp 202 204 —Ed]

DISEASES OF THE PLEURA

Chylothorax. Chylothorax is presence of a milky fat containing fluid in the pleural space it occurs when chyle escapes from the thoracic duct or its radicles and is the result of trauma to the duct or obstruction of the duct or great veins emptying into it Arthur M Olsen and George T Wilson (Mayo Clinic) believe that it is not uncommon and should be looked for as a complication of war injuries

Chylothorax should be suspected when pleural effusion follows thoracic injuries or when there is no explanation for pleural fluid in nontraumatic cases The aspirated pleural fluid is milky white and when dropped on a glass slide of oily appearance A creamy layer may develop at the top of the tube after standing Sudan III discloses the fatty nature Specific gravity is over 1 012 There are numerous cells with lymphocytes predominating The fluid clears when alkalinized and shaken with ether Total fat content varies from 0 4 to 4 per cent Chylopericardium and chylous ascites may occur with chylothorax

Treatment is not satisfactory Measures are directed to maintain nutrition and to replace serum proteins and fats lost in the chyle by high carbohydrate high protein diets There are reports of reintroduction of aspirated chyle into the venous circulation in hope of preventing peripheral edema Sodium citrate or heparin must be used as anti coagulant Solution of acacia or plasma given intravenously appears a safer method of restoring normal osmotic pres sure in the blood Thoracentesis is necessary for relief of acute respiratory embarrassment It is not always desirable to try to keep the pleural space empty by repeated thora centesis as the fluid tends to reaccumulate rapidly In about 50 per cent of patients with traumatic chylothorax the ruptured thoracic duct heals in a few weeks and they recover completely Attempts have been made to close the ruptured thoracic duct by introduction of foreign sub

(5) J Th ra S g 13 53 62 F bru ry 1944

charges into the pleural space Successful results have been reported after introduction of sterile broth or gomenol into the pleural space One patient with traumatic right chylothorax was cured after interruption of the phrenic nerve Elevation of the diaphragm presumably closed a perforation of the duct in the lower part of the thorax Roentgen therapy used for nontraumatic forms is most valuable when chylothorax is secondary to malignancy especially lymphoblastoma Prognosis in nontraumatic cases is generally poor as the underlying disease is usually serious In some cases no obvious etiologic factor is demonstrated possibly some trauma is responsible but malignancy must always be kept in mind

Relief of Acute Pleuritic Pain by Intercostal Nerve Block Harry J Price (Emory Univ) describes a procedure using procaine hydrochloride It is simple and effective often producing permanent relief of pleural pain associated with pneumonia It allows relatively free motion of the thoracic wall and so favors adequate aeration of the lung Drainage of the involved area of the lung is promoted for coughing is rendered less painful which is an added advantage in patients in whom sputum is difficult to obtain Chest binders and adhesive taping are avoided

METHOD —The nerves to be injected correspond to the intercostal spaces exhibiting definite tenderness on slight pressure The injection is usually made in the posterior axillary line or anterior to this if hyperesthesia is located more posteriorly it is made in the midscapular line A procaine hydrochloride wheal is first produced in the overlying skin A 20–21 gage needle is then introduced through the anesthetized area until contact is made with the outer border of the rib immediately above the selected space The periosteum is anesthetized with a few minims of the solution after which the needle point is carried down to the inferior margin of the rib where it falls into the groove occupied by the intercostal nerve and vessels At this point traction is exerted on the plunger until it is ascertained that the needle has not entered a vessel If no blood is drawn the nerve is infiltrated with 2 cc of a 1 per cent solution of procaine hydrochloride

Thirteen patients with pneumonia and one with pul

(6) J A M A 1 3 628 629 No 6 1943

monary infarction with severe lancinating pain were thus treated all but three of the pneumonia patients had audible friction rub Pain was relieved in all in 5–10 minutes after the injection and recurred in only two patients One of these was relieved by reinjection the other had to be given morphine in addition Most patients had tachypnea and in these the respiration became deeper slower and more regular with obliteration of the respiratory grunt

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ASTHMA DISEASES OF THE BRONCHI

Pathologic Anatomy of Bronchial Asthma. C Wegelin (Bern) reports two cases with emphasis on the micro



F 38 —W l g m h d b h l × 300

scopic changes in lung tissue affected by asthma The morphologic changes consist characteristically of desquamation of epithelium filled with mucus hyaline thickening

(7) S h m d W l h 4 5 8 J 8 1944

of the basal membrane hypertrophy of the elastic longitudinal fibers and circular muscles, severe infiltration of the mucous membranes and peribronchial tissue by eosinophil leukocytes herniated widening of the ducts of mucous glands and unusual development of the mucous glands The lumen is filled with tenacious sometimes spirally turned mucous masses containing very fine peculiarly formed threads first described by Marchand (Fig 38) The hypertrophy of the circular muscles is caused by bronchospasms and is not found in all cases of bronchial asthma Apparently therefore there are cases of asthma in which only the hypersecretion of tenacious mucus is responsible for the individual attack

Case of Bronchial Asthma Due to Aluminum Dust. Since Evang in 1938 noted increase of bronchial asthma in Norwegian aluminum workers no further observations of this phenomenon have been reported Lawrence H Cotter (New York City) reports a case.

A worker in an airplane factory whose job consisted of boring holes in aluminum plates complained of tightness in the throat which was relieved on leaving the plant In nine months he had lost 27 lb and the tightness in the throat had devel ped into definite attacks of difficult breathing while in the plant He also noted itching lesions on hands and arms and edema under the eyes these symptoms also subsided when he went home He was given a job in the yard where aluminum dust was less concentrated but without relief His chest was large and moved as a whole with respirations the costal angle was obtu The percussion note was generally hyperresonant The area of cardiac dulness was obliterated Breath sounds were distant and expiration was prolonged and low in pitch Blood showed 5 500 000 red cells and 20 Gm. hemoglobin (Sahli) which was unexpected in an undersized subject in ill health Four months after last exposure in the plant he appeared for a confirmatory test He had no asthma at the time Taken in a small room sprayed with aluminum dust there immediately developed an acute attack of bronchial asthma with cyanosis distended neck veins and wheezing in the chest all of which were relieved on leaving the room The patient is regaining his health in another occupation

(8) J I dust. Hyg & T c l. 25 421 N mbe 1943

Bronchospasm Associated with Pulmonary Embolism Norman H Boyer and John J Curry (Boston Univ) observed tran ient bronchoconstriction in dogs after induc tion of pulmonary embolism Its clinical importance is in doubt Bronchoconstriction appears to be a reflex mediated over the vagus nerve the afferent impulses are dependent on a rise in pressure in the right chambers of the heart

Drug therapy may have some value Atropine apparently prevents bronchospasm while papaverine produces transi tory constriction and both should be used in treatment of pulmonary embolism Digitalis in the form and dosage used in the experiments had no appreciable effect on the bronchi It can and should be used when there is auricular fibrilla tion or congestive heart failure without fear of possible harmful effects on the bronchi Epinephrine should not be used as bronchial antispasmodic because of ready produc *tion of pulmonary edema*

Death of the animals was usually due to respiratory failure This is inextricably bound up with failure of the circulation Agents most likely to support both circulation and respiratory center are oxygen papaverine and drugs capable of raising the systemic blood pressure without pro ducing undesirable side effects such as ephedrine Depres sion of the center by injudicious use of opiates or barbi turates must be avoided Some of the newer pressor drugs such as paredrine and paredrinol may prove even more suitable than ephedrine to improve the blood supply to the heart and medulla

[See Jes er and de Takats 1943 YEAR BOOK OF GENERAL MEDI CINE p 192—Ed]

Diagnosis of Bronchiectasis in Young Adults William A Evans Jr and Leon J Calinsky (M C A U S) re port on prebronchographic roentgen manifestations ob served among military personnel Of 95 cases frank bronchiectasis was seen in 37 minimal or questionable bronchiectasis in 24 and no bronchiectasis in 34 (see Table) In all bronchograms had been made and pre

(9) A ch I t M d 73 403 409 M y 1944
(1) Am J Roe tg l 51 537 54 M y 1944

bronchographic roentgenograms were available for examination

Concerning prebronchographic roentgen evidence of bronchiectasis, most initial films showed evidence of a basal bronchopneumonic infiltration Often symptoms were

INCIDENCE OF PREBRONCHOGRAPHIC SIGNS

Sign	Bronchiectasis					
	None		Minimal		Frank	
	Most Prominent Sign Only	Additional Signs	Most Prominent Sign Only	Additional Signs	Most Prominent Sign Only	Additional Signs
None	3		2		1	
Slowly resolving pneumonia	17	11	12	14	20	[illegible]
Prominent pulmonary markings	13	20	10	13	8	29
Recurrent pneumonia	1	2			6	6
Contracted lung	0	3	0	3	2	11
Total	34		24		37	

mild and appearance of lesions would have warranted the diagnosis of primary atypical pneumonia but usually such lesions resolved completely in 10–14 days When they show only partial resolution in two weeks and persist for three or four weeks or longer bronchiectasis should be strongly considered Slowly resolving bronchopneumonia was seen in 28 of the 37 cases 14 of the 24 cases and 11 of the 34 cases A less definite but frequent sign of bronchiectasis was accentuation of bronchial markings in basal and peripheral lung fields interpreted as peribronchial infiltration A less common but dependable sign of bronchiectasis was pneumonia recurring in the same area of the lower lung fields after a few weeks or months An area of contracted lung probably atelectasis resulting from fibrosis of the involved [illegible] was seen in 11 of the 37 cases

4 cases

Comparisons of the films show that bronchiectasis as demonstrated by bronchography can be predicted with reasonable accuracy from a study of the prebronchographic films Fairly close correlation was observed in 32 cases with frank bronchiectasis in 21 with minimal or question able bronchiectasis and in 26 in which no bronchiectasis was discovered

[See also Grier this YEAR BOOK p 187 Bronchiectasis should always be suspected when auscultation reveals persistent rales in a section of the lung in which the roentgenogram shows a clear or almost clear parenchyma —Ed]

Sulfonamides in Bronchial Secretion Effect of Sulfonamides in Bronchiectasis Charles M Norris (Temple Univ) studied the relation between concentrations of the sulfonamide in bronchial secretion and in blood after oral administration of sulfadiazine in 12 persons with acquired bronchiectasis Specimens of bronchial secretion were obtained by bronchoscopy at intervals of one to four days and blood samples were taken at the time of bronchoscopy A modification of the Bratton and Marshall method of quantitative determination of sulfonamide concentration applicable to bronchial secretion was used Concentrations of sulfadiazine in bronchial secretion ranged from 1 8 to 11 6 mg per cent with corresponding blood levels of 3 9–16 4 mg Average ratio of bronchial/blood concentration was 0 58 with an average variation from the mean of 0 08 or 14 per cent The values obtained in patients with scanty secretions did not differ materially from those obtained in patients with copious secretion nor did the values differ much in patients with saccular from those in patients with fusiform or cylindric bronchiectasis

The sulfonamide concentration in bronchial secretion following intratracheal or intrabronchial instillation of a 5 per cent suspension of microcrystalline sulfathiazole or a 2 5 per cent aqueous solution of sulfadiazine was observed in 10 patients with bronchiectasis Specimens of bronchial secretion were obtained by bronchial aspiration

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at the end of 24 hour intervals Values obtained with sulfathiazole were greatest 24 hours after instillation in patients with the smallest amounts of expectoration In two appreciable amounts of sulfathiazole were found after 48 hours In none of the cases following instillation of sulfadiazine were there significant amounts of the sulfonamide after 24 hours regardless of the amount of sputum being produced at the time of instillation presumably because sulfadiazine in aqueous solution is more rapidly eliminated by absorption and expectoration than the suspension of microcrystalline sulfathiazole

Ten patients with acquired bronchiectasis were given sulfadiazine by mouth in courses of 10–15 days To improve bronchial drainage bronchoscopic aspiration was performed at intervals of two to four days during the same period Blood levels were maintained between 8 and 12 mg per cent The outstanding effect was a definite and marked decrease in daily sputum volume varying from 55 to 81 per cent average 69 per cent The bacterial flora was also favorably altered although proper evaluation of this change was difficult This plan of treatment should prove of definite value as a preliminary to lobectomy or pneumonectomy for suppurative disease to lessen the possibility of aspiration into the good lung and to eliminate partially the risk of postoperative atelectasis or pneumonitis It is probably worthy of trial in cases of well established nonsurgical bronchiectasis

[The sulfonamides as well as penicillin often have some effect in temporarily controlling inflammatory lesions associated with bronchiectasis and preparing the patient for lobectomy Trials are being conducted of administering the drugs by inhalation but it is still uncertain whether this offers any advantage over the usual method of administration —Ed]

THERAPY AND MANAGEMENT OF VARIOUS RESPIRATORY CONDITIONS

Control of Acute Infections of the Respiratory Tract Morris Siegel (New York City) reports on use of sulfadiazine for common acute respiratory illnesses among highly susceptible children observed for 18 months to May 1943 The illnesse were milder generally in the drug treated groups than in untreated controls except during outbreaks of uncomplicated infections presumably of viral origin and in sporadic infections occurring during the e periods The beneficial effects were attributed to the bacteriostatic action of sulfadiazine on the susceptible bacteria primarily or secondarily involved The extent of the differences observed between untreated and treated groups varied considerably and depended largely on the nature and severity of the infections The beneficial effects of drug therapy were measured by reduction in duration of fever frequency of primary or secondary rises in temperature during illness and number of patients requiring hospitalization after the first day s treatment Usually at least 24 hours passed before the clinical effects of the drug were clearly noticeable

Although severity of the illnesses in the control group fluctuated with the year to year variations in severity of infections prevalent at the time the infections in the treated group appeared to be relatively mild during the period of observation The drug therefore appeared to exert a stabilizing effect on the course of acute infections of the respiratory tract Such an effect might prove of value during severe outbreaks of influenza and other respiratory diseases due to drug susceptible bacteria

Comparison of Four Routine Procedures in Treatment of Acute Catarrhal Fever James J Short Lawrence O Toomey Edward W Schoenheit Frank R Smith Jr and George W Slagle studied these measures in 827

(3) Am J Dis Child 67 365 370 May 1944
(4) U S Nav M Bull 4 848 851 Ap 1 1944

patients Treatment for group 1 the controls consisted of only general measures and nursing care such as bed rest abundant fluids during febrile periods sedatives codeine and laxatives when indicated Each patient was given a placebo capsule of milk sugar every four hours In group 2 these measures were followed except that two capsules were given every four hours each containing 3 gr aspirin 2 gr phenacetin and 1 gr caffeine citrate plus elixir of terpene hydrate and codeine when necessary for cough In group 3 in addition to the general measures 2 Gm sulfadiazine was given on admission followed by 1 Gm every four hours until temperature was normal for 48 hours In group 4 treatment consisted of the general measures plus a special capsule containing 1/2 gr codeine sulfate and 3/8 gr ephedrine sulfate three times daily after meals and two at bedtime Evaluation of methods was based on the average febrile and hospital periods and clinical impression

The shortest average febrile and hospital periods were obtained in group 3 the next shortest periods in group 2 and the longest periods in group 4 Despite this low score for group 4 the medication made the patients more comfortable than those in the other groups The medication given in group 2 promptly relieved aches and pains frequently associated with catarrhal fever and thus afforded comfort and well being even though the average hospital and febrile periods were about a half day longer than in group 3 A distressing side effect however was the tendency to produce drenching sweats which necessitate frequent change of garments and may cause chills The risks attendant on sulfonamide treatment which gave the best results in this study may be combated by adequate fluid intake and use of sufficient alkali to keep the urine at a pH of 7 5 or above to prevent urinary complications with the average dose The occasional skin reaction due to idiosyncrasy is mild and recedes on withdrawal of the drug The saving of time in sick days

and the almost certain prevention of more severe pulmonary complications in a certain percentage of cases of catarrhal fever make the sulfonamides the measure of choice for routine therapy Combining the results from all groups and weighing relative advantages a combination of sulfadiazine therapy with routine use of sufficient codeine to make the patient comfortable together with general measures and good nursing care apparently constitutes the best treatment available at present

[[illegible] of the sulfonamides [illegible] medication particularly over a long period is widely deprecated since this may favor drug fastness of invading micro organisms as well as tissue hypersensitivity to the drugs —Ed]

Chronic Pulmonary Catarrh in Childhood A Brian Taylor (Birmingham England United Hosp) states that the term chronic pulmonary catarrh describes a clinical syndrome common in children which causes recurrent respiratory attacks often suggestive of asthma but associated with inflammatory lung changes In some children the attacks are mild and are referred to as bronchial colds with slight pyrexia and cough in others the asthmatic features predominate with labored wheezy breathing and prolonged difficult expiration Again a mild pneumonic attack may appear Duration and termination vary although the slowness of resolution and of disappearance of cough is most noticeable The acute asthma picture often lasts several days and is followed by persistent wheezing and a cough especially troublesome at night or increased by exertion with extrarespiratory activity Prolonged expiration is usual but rapid shallow breathing is not uncommon Rales and rhonchi may be heard anywhere but especially posteriorly and almost always bilaterally Between attacks the child may be quite well but there is usually shallow breathing poor development of the thorax with round shoulders flattening anteriorly and Harrison s sulcus and coughing after deep breathing or exertion Pharyngitis is often present

[illegible] Ap [illegible] 1944

and possibly infected tonsils and postnasal catarrh However cure of upper respiratory infection does not necessarily prevent recurrent pulmonic attack

Roentgenographically movements of the diaphragm are usually restricted In patients with an asthmatic tendency the thoracic cage is deformed the ribs having an upward tendency from excessive inspiratory efforts The chest tends to rise on inspiration instead of expanding The lung roots are unduly heavy suggesting glandular enlargement The striations radiating therefrom are thick and increased especially to the lower lobes but often into all zones The parenchyma may have a slightly woolly appearance The bilateral and symmetrical nature of the changes is of importance During or immediately following an acute exacerbation there may be shadows of pneumonic consolidation in some parts of the lungs later films will show them to have disappeared

In differential diagnosis true asthma bronchiectasis and tuberculosis must be considered

In the acute attack treatment is that of acute bronchitis asthma or pneumonia, depending on predominant features. Frequency of attacks and permanent damage must be considered In peacetime wintering in Switzerland for several years proved most satisfactory proving that climatic measures give good results There seems to be a tendency for the child to grow out of the condition or at least the susceptibility to it as he reaches adolescence if the ill effects can be prevented by avoiding attacks for some years much of the danger has gone Breathing exercises to correct faulty posture and movement of the thoracic cage promote diaphragmatic movement increase respiratory excursion and resilience and improve expiration are valuable Insistence on nose breathing can obviate much of the reinfection and recrudescence of infection from the pharynx Group teaching of exercises is best as it develops the team spirit encourages regularity and initiates new patients Treatment must be continued for months or years and parents must be taught the elements

Results include fewer and shorter attacks better health between attacks loss of cough and less susceptibility to catarrhal infections

Expectorant Action of Paregoric Eldon M Boyd and Marion L MacLachlan (Queen s Univ Kingston Ont) investigated the expectorant action of paregoric by measuring its effect on output of respiratory tract fluid (R T F)

Paregoric increased the output of R T F in albino rats cats rabbits guinea pigs and hens and would therefore probably have the same effect in man Experiments with the components of paregoric—tincture of opium camphor benzoic acid oil of anise and alcohol—regarding their individual effects on the output of R T F showed that all increased the amount When combined however the ingredients of paregoric had a more prolonged effect on output than that obtained by a summation of the effects of the individual ingredients On further testing this synergistic action was not seen with freshly prepared paregoric or with paregoric which had aged less than one year It was seen best in preparations which had been aged well over one year and were dark brown in contrast to the pale and light brown color of nonaged preparations

Investigation of the mechanism of the expectorant action was made in animals in some of which the afferent vagal nerves of the stomach had been severed Albino rats with gastric nerves intact showed the usual response although output was somewhat less than that previously obtained probably because the paregoric was not as old as that previously used and possibly because of manipulation of the intestine Paregoric to rats with gastric nerves severed did not augment output indeed there was decrease The conclusion therefore is that the effect of paregoric on output of R T F is due to a reflex from the stomach

Because of various reports on action of morphine on gastric and intestinal movements blood pressure pupil of the eye cholinesterase etc particularly one that recorded that pilocarpine and cervical vagus nerve stimulation aug

( ) C d M A J 50 338 344 Ap 1 1944

mented output of R T I the authors investigated the effect of morphine on output of R T F Morphine hydro chloride 1 mg per kg body weight injected subcutaneously into 10 albino rats did not affect the rate of output of R T I Twelve others given 0 05 mg physostigmine salicylate per kg subcutaneously followed by 1 mg morphine hydrochloride showed no effect on output of R T F

A New Apparatus for Administration of 95 Per Cent Oxygen is described by Meyer Saklad and Alexander M Burgess (Rhode Island Hosp Providence)

APPARATUS —This consists of a closed oxygen box of the usual type without the tray of soda lime formerly used Instead of eliminating carbon dioxide by such a tray inside the box the respired atmosphere is circulated through a cylinder



Fig 39 —Apparatus in use

of soda lime outside the box Instead of using a motor blower which would increase the cost and incur fire hazard the injector principle is used As the oxygen leaves the cylinder under great pressure it is passed through a venturi valve creating a negative pressure in a side tube. Thus the flow of oxygen not only serves to satisfy the patient s oxygen requirements and maintain the desired 95 per cent concen

(7) J A M A 1 4 8 183 M 25 1944

tration but also satisfactorily produces a circulation through the soda lime which reduces the carbon dioxide in the box to about 1 per cent The venturi valve creates varying degrees of negative pressure dependent on the flow

The availability of this inexpensive and satisfactory method of developing and maintaining high nitrogen free atmospheres should encourage use of this type of therapy in conditions in which nitrogen removal from tissue may be advantageous

[A small efficient hood for oxygen therapy is also described by Lambertson and Codfrey (*Journal of the American Medical Association* 125 492-493 June 17 1944—Ed.]

Immediate Care of the Unconscious Patient. Hubert R Hathaway (Univ of California) states that respiratory obstruction is the immediate cause of death in many unconscious or semiconscious persons even though partial or complete occlusion of the air passages is preventable in almost every instance The commonest form of respiratory obstruction is in the upper tract and is caused by relaxation of the muscles of the tongue and pharynx allowing the soft parts to fall back into the posterior pharynx Stertorous breathing indicates this type of obstruction To prevent it the mandible is raised and brought forward so that the tongue and soft parts are displaced away from the posterior pharynx The next most common form of obstruction in the upper tract is collection of secretions mucus blood vomitus and the like The protective mechanisms such as expectorating swallowing or coughing are lost in the unconscious subject Wiping the material out with the finger covered with gauze is advisable but not completely effective in most instances The patient can be placed in the Trendelenburg position so that the material will drain into the nasopharynx or he may be rolled onto his abdomen thus allowing the foreign material to drain out and also permitting his tongue to fall forward The so called Sims tonsil or cerebellar position is best because with minimal adjustment it clears the airway and keeps it clear by gravity

(8) J N & M t D 99 636 639 M y 1944

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Fg 39—App t s n use

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(7) J A M A 1 4 8 1 8 3 M 25 1944

this the best most easily accomplished means of con tinuous artificial respiration available A tilter or a door or plank on a trestle is a satisfactory substitute but the tilting movements must be at least 45 degrees each way to make real use of gravity

The Bragg Paul pulsator is the best of many devices which provide mechanical imitation of the prone pre sure

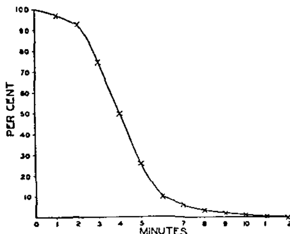


Fig 40—Cha s of ecov y ft t f b eath g p d d m pet t tifi l p t g n.

procedure It has given good results in protracted treat ment of respiratory arrest from poliomyelitis postdiph theric paralysis morphine and barbiturate poisoning and other conditions It is simple inexpensive and well toler ated by conscious patients It seems to be most useful in assisting patients who are losing their power to breathe but retain some ability to assist the apparatus Blow and suck machines of various kinds are efficient but not physiologically as suitable as other methods

Oxygen or air enriched with oxygen as much as pos sible should be given in all cases of asphyxiation If oxygen can be supplied to the blood life may continue

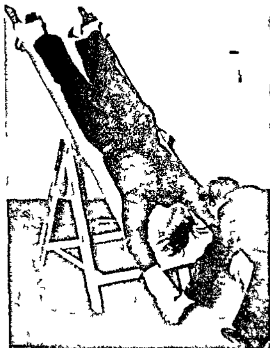
The patient remains in place as his upper knee is flexed supporting him and making the use of pillows unnecessary In this posture he may even be left alone for short periods with more safety than in any other position The unprotected unconscious patient must never be placed in the sitting position because this permits drainage into the larynx and from there into the lungs

Restoration of Breathing in Emergencies and Maintenance of Respiration in Nonbreathing Patients Cecil K Drinker[9] (Harvard Univ) emphasizes the speed with which artificial respiration must be given to prevent further asphyxial damage and death (Fig 40) The Schaefer and Sylvester methods give excellent emergency service in the field and often in the hospital with physicians as operators For patients under anesthesia and on the operating table mouth to mouth insufflation can be done or oxygen can be administered through the ordinary mask and rubber bag of the anesthetist The chest must be watched and felt to ascertain that oxygen is actually entering the lungs the prone position with the head down permits drainage of air passages

Protracted artificial respiration is more difficult Manual methods all cause forcible expiration by manual pressure which decreases size of the chest by forcing the abdominal contents up against the diaphragm and narrowing the lower part of the thoracic cage through inward and upward movement of the lower ribs When pressure is released the elastic recoil of the parts causes inspiration With Eve s tilt technic air is forced out of the chest by an upward push of the diaphragm by the abdominal contents followed by maximal passive descent of the diaphragm when the head up swing reverses the movement of the abdominal contents If pressure is applied as in the Schaefer method during the head down swing ventilation and clearance of air passages *will be improved* Furthermore the rhythmic head down position is exceedingly beneficial to the circulation Drinker considers

(9) J Okl h ma M A 7 285 93 J ly 1944

heart is simplified into two rubber syringes The one way valves in veins and heart are shown *C* indicates the coronary artery which carries oxygenated blood from the main artery through the actual muscles of the heart to join blood flowing back into the lungs On tilting into the head down tilt pre sure ot about 4 ft of blood in



I g 41 —I k g t tl (C p ght by G H G bbe F I w S d m th D England)

the arteries will shut the main (aortic) heart valve and must travel through the oxygen starved heart muscle This should be invaluable in starting a stopped heart or restoring a feeble one Similarly nerve cells of the brain

and pure oxygen has five times the efficacy of air Carbon dioxide should not be used in concentrations higher than 7 per cent oxygen rather than air should accompany the carbon dioxide Respirators of various constructions will always save some lives but there are many they will not save

Resuscitation of the Drowned Frank C Eve (Hull England) states that resuscitation of the drowned is not merely working the bellows of the lungs but a fight to revive cold asphyxiated nerve cells by circulation of warm blood oxygenated by moving lungs The Schaefer method is inadequate the Sylvester and the recent rocking method are in many ways better Eve stumbled on the rocking method by accident and physiologic experiment showed its efficiency at 10 double rocks a minute with a tilt of 50 degrees to ventilate 600 cc per rock more ventilation would introduce the possible dangers of acapnia The method was adapted to ships of the Royal Navy by fixing under the middle of an ordinary stretcher a pair of grooved wooden blocks to prevent slipping On these the stretcher can be rocked 45 degrees each way on a trestle 34 in high or on a loop of rope (Fig 41)

PROCEDURE—Schaefer's method is used until rocking can be started The patient is laid face down and ankles and wrists are locked to the stretcher handles The first head down tilt of 45 degrees is maintained until no more water drains from stomach or lungs After a few minutes a tilt of 30 degrees each way (10 times a minute) is enough to ventilate the lungs During rocking wet clothes are removed and heat is applied

Advantages are that untrained operators can be used it does not injure ribs or viscera and is independent of muscular tone in blood vessels or diaphragm in which respect Schaefer's method fails

Figure 42 represents the circulation Since gravity in rocking affects only the longitudinal blood vessels they are represented as straight tubes arms and head are omitted as they are counterparts of legs and trunk the

(1) J A M A 1 4 9(4 9(Apr 1 1944

of oxygen uptake and cardiac output is usually greater with the rocking than with the Schaefer method the O tension of the venous blood is higher —Ed]

Rehabilitation of Chest Case F Ronald Edwards[2] (Univ of Liverpool) believes that rehabilitation centers can restore most patients to a high degree of fitness in a remarkably short time This belief is based on a study of a large group of chest cases both medical and surgical which were under personal supervision all the time The essential feature from the patient s viewpoint is that something is being done for him He is guided and urged to further efforts throughout his convalescence by instructors *and by the example of his colleagues the competitive* element and team spirit are of some importance Exercises must not be overdone as fatigue particularly in the early stages may soon develop Unless the patient has fully recovered from fatigue before the next exercises are done they become a burden consequently they are inefficiently done and recovery is slowed Rehabilitation must not be forced

Causes of disability include weakness and inefficiency of the respiratory musculature damage to the bony structures of the thorax thickening and adherence of the pleura pulmonary fibrosis loss of lung tissue emphysema and finally pain On admission to the center a full history is taken and clinical examination made with roentgenography A spirographic curve is taken to give information on tidal air pulmonary ventilation in liters per minute at rest vital capacity complemental air supplemental air maximal breathing capacity and evidence of inherent pathologic process The patient is then classed for exercises and assigned to a particular group As he progresses he is put into higher grades A continuous check is kept on improvement by vital capacity readings chest and abdominal expansion measurements and fluoroscopy When he approaches his maximal degree of fitness a standard exercise test is made and cardiopulmonary efficiency estimated by the mercury U tube

(2) L et 1 81 84 J 15 1944

and breathing center receive blood rhythmically at hydrostatic pressure calculated to be normal Veins of the extended arms acquire a reservoir of blood ready to fill the heart again when the legs are tilted down Every drowning person is shocked and in shock the venous side of the heart is starved of blood In that case the head down tilt will fill it and encourage it to beat and pump On tilting feet down blood falls from the lungs past the open valves of the left side of the heart into the arteries of trunk and legs Hence in rocking gravity propels the blood alternately in arteries and veins in the direction of the arrows reflux is prevented by valves in the veins and heart Physiologic experiments confirmed that blood flow to the brain can be maintained by head up and head down positions alternated

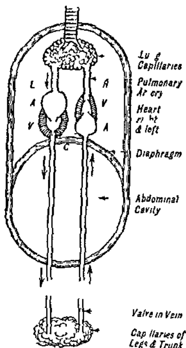


Fig 4 —Diag m f c l t on

Heat loss must be prevented Eve suggests hot water bottles saddle bagged over the neck or an electric shock cradle tied to the head end of the stretcher Hot water might be poured over head neck and heart Carbon dioxide inhalation with 5 per cent oxygen used in resuscitation because it stimulates respiratory nerve cells has been abandoned because it is a dangerous depressant to nerve cells of those at the point of death

[From experimental evidence Hemingway and Neil (*British Medical Journal* 1 833 836 June 24 1944) conclude that the ratio

examination alone and by the patient s symptoms but physiologic investigations and exact figures are valuable.

Treatment of Silicosis by Aluminum Powder D W Crombie J L Blaisdell and G MacPherson (London Ont) report a three year investigation based on the work of Denny Robson and Irwin who showed that silicosis can be prevented in animals by inhalation of small quantities of metallic aluminum powder Only men still exposed to silica dust in gold mines were considered and only those with uncomplicated silicosis with measurable pulmonary disability were chosen

The original investigators decided that to be effective metallic aluminum powder must be of a particle size comparable to that of the dangerous silica particle i e under 5 microns in diameter The powder is manufactured directly before inhalation and administered while still suspended in the atmosphere in its original finely divided state A specially constructed mill is used to grind the aluminum

APPARATUS—The mill consists of an aluminum cylinder or drum 12 × 12 in mounted on a 3⁄4 in hollow shaft This shaft inside the mill has many small perforations on either side of a short central peng or core which prevents inspired air from being drawn directly through the shaft without entering *the cylinder The latter is enclosed in a wooden box lined* with sound absorbing material The shaft is connected by a perforated cam to a 20 1 reducing gear operated by a 1⁄4 hp electric motor rotating the drum or cylinder at about 80 rpm All operating parts are well grounded. The opposite end of the hollow shaft is connected with a 12 L glass bottle which serves as a sedimenting chamber where the coarser particles settle out A charge of 25 lb chemically pure aluminum pellets sheared from 3/16 in aluminum rod and measuring about 3/16 in long is placed in the drum one end of which is removable A small amount of aluminum *powder is introduced with the pellets as a primer to* facilitate the grinding process in a new mill Before use the mill should be operated for several hours daily for a few days until maximal efficiency is reached In general at an airflow rate of 10 L per minute through the mill about 2–3 mg

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Instruction begins with correct breathing Patients in the surgical unit are immediately taught the elements of individual costal and diaphragmatic breathing so they can perform the respiratory exercises as early as possible in the postoperative period usually the second or third day By use of hand pressure breathing with individual areas of the chest can be practiced Patients admitted to the center without having been through the surgical unit receive a similar course of instruction at a preliminary grade with emphasis on developing expansion of the chest area that has been pathologically affected The next grade introduces shoulder and scapular movements and side bending and rotating movements of the chest to develop the accessory chest musculature and respiration and to stretch and free intermuscular and periarticular adhesions General fitness exercises are added with bicycle riding pulley and weight machines punch ball wall bars skipping and ball throwing football and goal kicking are valuable Later planned runs starting at 200 yds and working up to 2 miles or more are made over a rough circular field track with the instructor keeping constant watch The instructors are trained to note first signs of distress Pulse rate is taken before immediately after and five minutes after completion of the run The rate should return to about normal after five minutes if full fitness has been attained but with longer runs this may take up to 10 minutes The courses are given in the morning with the afternoons occupied by walks in the country and recreational activities A week s leave in the middle of the course should not be refused Change of surroundings is valuable and improves mental tone despite the almost inevitable fall in respiratory efficiency during leave

Management of the center by women physiotherapists has been found completely satisfactory Massage is given when necessary and ultraviolet light baths in winter Improvement can be assessed during the course by clinical

followed by beneficial results in many cases chiefly shown in amelioration of symptoms and in increased capacity to work The authors believe therefore that inhalation of fine particles of aluminum powder offers every prospect of preventing development of human silicosis

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DIAGNOSTIC METHODS AND SIGNS

Technic for Examining Exudates (Pleural, Pericardial Ascitic) Especially for Carcinoma and Tuberculosis *is described by R Massini (Univ of Basel) The* formation of coagulums greatly impedes study of serous exudates and these coagulums enclose a considerable proportion of corpuscular elements (cells bacteria) which may escape detection The cells cannot be separated from the fibrin network even by centrifugation and the bacteria *especially tubercle bacilli cannot be recovered for culture* or drawn into a syringe for animal inoculation without dissolving the coagulum in sulfuric acid or antiformin which procedure might damage the organisms

This difficulty may be overcome by adding to the punctate 0 79 per cent sodium citrate or some other anticoagulant The 3 8 per cent sodium citrate solution used for determination of erythrocyte sedimentation rate may conveniently be used in proportions 1 5 = 1 + 4 For detection of malignant tumor cells the citrated exudate instead of being centrifuged is best allowed to stand in the tube until a sediment forms This sediment is loose and there is no clumping the cells can be differentiated microscopically Good pictures are obtained which sometimes resemble explants The sediment can also be stained The cell aggregates can be seen under low or medium magnification whereas for accurate identification the higher dry lens systems are used best In urgent cases when the time factor counts the exudate may be centrifuged at low speed *to avoid clumping of blood cells*

An incoagulable exudate is still more desirable for

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aluminum powder per L air is produced. The powder is black and assays 20 per cent metallic aluminum and 80 per cent of oxide

TREATMENT—After the mill is warmed up the patient is connected to the 12 L bottle by a 1 in rubber tube to which is attached a double Douglas valve to prevent rebreathing into the system and another short piece of rubber tubing with a metal mouth piece The nose is clamped slightly As he inspires air enters the shaft through the perforations in the cam and is drawn into the interior of the cylinder through the small perforations in the shaft Here the air becomes charged with powder and is drawn back into the shaft through the perforations on the other side of the center peng The powder laden air enters the bottom of the 12 L bottle where the coarser particles settle out only the finer ones entering the outlet tube at the top of the bottle Treatments were begun with a five minute inhalation daily This was increased by five minutes every few days until at the end of about a month 30 minute periods daily were given Treatments were continued six days weekly until about 200 treatments were given A few patients received as many as 300 This is probably more than is necessary and later the number was again reduced

Aluminum powder is harmless and proved definitely beneficial in some of the cases Of 34 patients who completed the course of therapy 19 showed clinical improvement apparent chiefly in the lessening or disappearance of shortness of breath cough pain in the chest and fatigue A reduction in incidence of colds and a gain in weight were observed While 15 cases remained stationary it is emphasized that they were no worse and did not progress despite continuous employment of the patient in silica dust during the investigation Respiratory function tests repeated about every three months showed improvement in 12 cases

Twenty two remained stationary despite continuous exposure to silica dust Of nine controls untreated by aluminum 66 per cent showed progression of their disease while under observation

Aluminum dust cannot be regarded in any sense as a cure for silicosis so far as restoration of fibrotic lung tissue to normal is concerned Its use however appears to be

[In this country culturing of specimens has largely displaced animal inoculation but this is justified only if the preparation of the mediums and the technic of handling the specimen are skilfully carried out —Ed]

Respiratory Shift in Epigastric Abdominal Wall Physical Sign Seen with Complete Unilateral Paralysis of Diaphragm in Infants and Children Jacob S Light (Johns Hopkins Univ) describes this sign which aids in recognition of such paralysis on physical examination

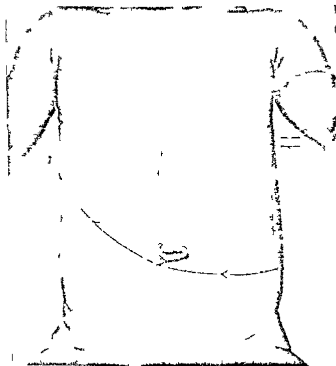


Fig 44 —P ly f ght l ph m how ng d pl ment t bd m l ll d p isp t D tt d l h w xt t f mo m t w t d t n.

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inflammatory reactionless process It occurs in the deep veins of the legs usually below the knees In its dangerous stage it causes little venous obstruction Although it may occur at any age and in an individual of any physical type it is most common in the sixth and seventh decades and in fat or fattish subjects The peculiar and dangerous quality of a quiet venous thrombosis lies in its decided tendency to form a loose soft detachable thrombus A fatal pulmonary accident may come from a leg appearing normal In contrast the great swollen leg of thrombophlebitis seldom causes embolism the inflammatory thrombus being fixed by local reaction in the wall of the vein In quiet thrombosis the original process may pursue one of three courses (1) recovery without extension (2) development into phlegmasia alba dolens and (3) formation of a propagating thrombus with pulmonary embolism John Homans (Harvard Univ) reports 11 cases of the last category and discusses 6 additional cases of embolism arising from thrombosis due to injury illness or old thrombophlebitis Two illustrative cases are presented here

Man 49 had had two episode of violent substernal pain on successive days three weeks previously with dyspnea and cough There was thrombosis in a varicose vein of the right leg associated with cyanosis and slight swelling of the whole right leg and indicating thrombosis as high as the inguinal ligament Operation consisted of division of the right common iliac vein no thrombosis was found at this level There was recovery with excellent function and no further embolism

Man 55 three years previously had experienced a supposed *coronary occlusion from which he recovered One week* previous to admission there was a sharp pleural pain on the left side X rays revealed a pulmonary infarct There was a positive dorsiflexion sign in the right leg but no cyanosis or edema Operation consisted of division of the right superficial femoral vein and periarterial sympathectomy No thrombus was found at this level Recovery resulted with no further embolism

In the idiopathic group were 9 men and in the entire

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In a new born infant on repeated occasions it was noted that with each inspiration the abdominal wall of the whole midepigastric region shifted markedly to the right and to some extent upward on the right describing a diagonal or arciform type of movement with the convexity of the arc down with each expiration there was a shift back to neutral position In this movement the whole thickness of the abdominal wall seemed to participate including the kin as demonstrated by a bit of adhesive tape placed over the mid epigastrium When the baby cried with resultant deeper inspiration the sign was even more marked The appearance of diagonal movement was accentuated by the fact that the costal margin on the right rose strongly with inspiration (Hoover s sign) while on the left there appeared to be descent The umbilicus and area immediately above it took part in this motion the xiphoid cartilage and area of epigastric abdominal wall immediately below it did not participate (Fig 44)

The sign was observed in four other cases of unilateral diaphragmatic paralysis This shift in the epigastric abdominal wall is possibly a corollary of Hoover s sign and is due to pull of the heightened inspiratory ascent of the costal margin on the affected side with associated widening of the subcostal angle and ballooning out of the costal margins themselves Three conditions limit appearance of the sign (1) One side of the diaphragm must be completely paralyzed as shown by paradoxical movement on fluoroscopy with the other side intact or nearly so (2) The sign appears in fully developed form only in infants and young children its failure to appear in adults is probably due to the relatively lesser increase in ascent of the homolateral costal margin attributed to the lesser degree of mobility of the thorax itself Abdominal muscles may also limit ascent of the costal margin and their relatively greater development in adults may be partly responsible for nonappearance of the sign (3) At least in children as compared with infants a deep breath must be taken

Pulmonary Embolism Due to Quiet Venous Thromboses and Simulating Cardiac and Pulmonary Disease Quiet thrombosis or so called phlebothrombosis is a non

DISEASES *of the* BLOOD *and* BLOOD-FORMING ORGANS, DISEASES *of the* KIDNEY

GEORGE R MINOT M D S D F R C P
(Edinburgh and London)

AND

WILLIAM B CASTLE M D S M
M D (Hon) Utrecht

series of 17 cases there were only 3 women Ages ranged from 28 to 63 only three of those with idiopathic cases were under 50 Multiple embolism occurred six times in the idiopathic group There seems to be no rule regarding seriousness of individual episodes In one case after many small embolisms had left no trace in the lungs verified by x rays an accumulation of many fragments coming from both legs and perhaps from the veins of both thighs finally despite division of the femoral vein plugged the pulmonary arteries with fatal result The other five re covered after vein division There was one fatal case among the five with single embolism In the secondary group multiple embolism occurred four times In three instances all of thrombosis following old femoro-iliac thrombophlebitis vein division was followed by recovery The fourth patient in whom infarction followed acute enteritis had heparinization alone and died

When an embolus causes a true anatomic pulmonary infarct a pleuritic type of pain results then there is little suggestion of angina or coronary occlusion But emboli do not necessarily cause demonstrable obstruction of a large or small pulmonary vessel and so are apt to cause substernal agonizing pain fainting or breathless ness or a combination of these symptoms A normal electrocardiogram is consistent with pulmonary embolism but serious obstruction of the pulmonary circulation i e cor pulmonale will give characteristic signs X rays are helpful in making a positive diagnosis of pulmonary in farction yet a clear lung field is consistent with serious and repeated embolism

Consideration of these cases shows that since infarc tion and embolism often simulate pulmonary and cardiac disease in ambulatory patients otherwise well they must be considered in differential diagnosis of many acute and recurrent thoracic disorders Treatment of choice is sur gery to secure interruption of the thrombosed vein proxi mal to the source of embolism conservative treatment does not prevent continuance or recurrence.

PART III

DISEASES OF THE BLOOD AND BLOOD FORMING ORGANS

GENERAL CONSIDERATIONS

The following articles are concerned with topics of a general nature or not appropriate to any particular section —Eds

Physiology of Hemopoietic System in Infants and Young Children, Including Blood Picture at Birth and in Young Infants is discussed by Pearl Lee (Detroit) The new born begins life with a blood picture peculiar to its age group Changes begin soon after birth and are especially striking the first six months By the end of the second year the picture is approximately that of the adult

The new born has a very high hemoglobin level and a moderately high red blood cell count with reticulocytes and a few normoblasts Cells more immature than the normoblast are pathologic in the full term infant but may occur in the premature The mean corpuscular diameter is large being 8 6 (adult average 7 2–7 4) White cell forming tissues are also active producing a total white cell count of 10 000–20 000 at birth there may be higher and lower values Myelocytes are rare in the full term infant but frequent in the premature The platelet count usually does not show great variations A few days after birth a rapid decrease in hemoglobin and red blood cells begins By the time the infant is 2 weeks old the hemoglobin level has fallen 3 or 4 Gm and the red cell count about 1 000 000 Normoblasts disappear in two or three days or a week at the most Reticulocytes also decrease This rapid fall reaches its lowest point usually by the eighth or tenth week The cell diameter also decreases to adult

(1) J Pediat 23 6 6679 December 1943

physiologic jaundice and increased pigmentation of the blood serum The most widely accepted mechanism for the rapid change in the blood has been this speeding up of the destructive process Hemolysis in the new born can easily become severe enough to produce an acute hemolytic anemia Sometimes it occurs as a result of infection or by immunization as in erythroblastosis foetalis

The lowest levels of hemoglobin and red blood cells are seen at 6 or 8 weeks Often reduction is excessive producing moderate anemia probably due to a mild hypoplastic state As administration of iron will not affect the blood picture before six or eight weeks the factors influencing the hemoglobin and red blood cells in the early weeks are probably physiologic or intrinsic After that time extrinsic factors such as diet administration of iron and infections become more important At 3 months the reticulocyte count rises slightly preceding an increase in the red blood cells The hematocrit index falls to 35 per cent the lowest normal limits at 6 months and remains near this level throughout childhood Between 6 months and 1 year there is little change in the blood picture At 2 years it approaches the adult standard

Studies in Protoporphyrin IV Comparison of the Erythrocyte Protoporphyrin Concentration with the Reticulocyte Percentage under Experimental and Clinical Conditions Watson and Clarke stated that the erythrocyte protoporphyrin resides chiefly if not solely in the reticulocytes This conclusion was based on finding of protoporphyrin (1) in the reticulocyte rich upper strata of centrifuged blood and (2) in samples of blood containing only reticulocytes C J Watson Moises Grinstein and Violet Hawkinson (Univ of Minnesota) report further observations

In five rabbits with acute phenylhydrazine anemia the curves of the reticulocyte percentage and erythrocyte protoporphyrin content followed each other closely The crystalline protoporphyrin isolated from the erythrocyte

(2) J Cl n. I t g t 23 69 80 J y 1944

size The white count gradually drops to an average of 10 000–12 000 at 6 months During the first two weeks there is a rapid shift in the differential from a high percentage of neutrophils to a preponderance of lymphocytes At age 2 the lymphocytes are still slightly in the majority

The high hemoglobin level and red cell count present at birth are developed during the last few weeks of fetal life The primitive red cells appearing early in the embryo are large and nucleated about the fourth month the formation of true red blood cells begins Concentration of hemoglobin and red cells is still low at this time Development of white cells occurs simultaneously with the second type of red cells in the bone marrow liver spleen and lymphatic tissues As the fetus develops there is slow increase in hemoglobin and red cells with reduction in cell diameter and number of immature forms These changes continue up to birth and for a few hours afterward

The blood forming tissue is extensive at birth Not only does red marrow fill the cavities of all bones but islands of erythrogenic tissue are present in liver spleen and most lymphatic tissues Production of erythrocytes and myeloid leukocytes in the extramedullary foci ceases immediately However the lymphatic organs continue to develop and are probably responsible for the preponderance of lymphocytes in infancy

The marked changes in the blood picture beginning in the first few days of life are no doubt due to the radical changes in the new born s environment The organism is as yet very unstable and the blood forming tissues share in this instability Trivial causes may produce wide fluctuations in the blood picture Sudden removal from a low to a relatively high oxygen tension may be the main mechanism initiating early and rapid decrease in hemoglobin and red blood cells This reduction must be accomplished by decrease in blood formation or an increase in destruction or both Evidence for decrease in production is indicated by disappearance of normoblasts and reduction in reticulocytes Increased destruction is manifested by

observed in posthemorrhagic iron deficiency anemia The amounts were also considerably increased in patients with hemolytic anemia and with certain toxic states but were relatively low and within normal range in untreated persons were pernicious anemia

Sterile incubation of blood samples from the patients and the animals for 24–48 hours revealed a regular increase in erythrocyte protoporphyrin despite the decreasing reticulocyte percentage The authors consider the possibility that erythrocyte protoporphyrin may be formed in vivo from hemoglobin under certain circumstances

The results of this investigation indicate that at least two factors in addition to the erythopoietic activity account for erythrocyte protoporphyrin (1) iron deficiency or interference with utilization of iron in hemoglobin synthesis and (2) hemoglobin degradation in intact blood cells

Effects of Sulfonamides on Blood Roy R Kracke (*Emory Univ*) *considers sulfanilamide sulfapyridine* sulfathiazole and sulfadiazine as these sulfonamides have been in use longest and therefore permit evaluation

The drugs produce similar if not identical effects on the blood The mechanism of cyanosis from sulfanilamide is unknown but evidence indicates that methemoglobin is partly responsible for the cyanosis plus actual staining of the blood cells by the purple oxidized drug The drugs are capable of producing serious degrees of acute hemolytic anemia This disorder is characterized by quickly increasing pallor usually fever and rapid decrease in red cells and hemoglobin There is evidence of increased red cell destruction increased icterus index urobilinogen and perhaps clinical jaundice There also occurs reticulocytosis a sign of increased red cell formation These signs demand investigation of the blood picture and discontinuance of treatment with sulfonamides

Agranulocytosis does not occur nearly as frequently as acute hemolytic anemia after sulfonamide administration

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was the isomer type 9 corresponding to aetioporphyrin III In eight patients with pernicious anemia studied before and at various intervals after liver extract therapy there was lack of correlation and in several instances even a marked divergence between the reticulocyte and protoporphyrin curves The differences were not correlated with the relative age of the reticulocytes as determined by the amount of substantia reticulofilamentosa In general

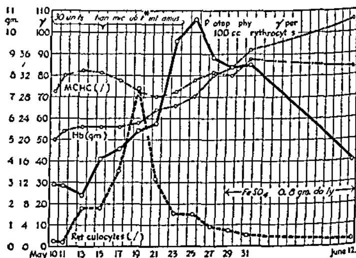


Fig 45 —Erythrocyte protoporphyrin concentration, reticulocyte percentage, hemoglobin in Gm per 100 cc. blood and hemoglobin concentration of erythrocytes before and after liver extract therapy in man 53 with pernicious anemia

the peak of the protoporphyrin curve was attained later than that of reticulocytes (Fig 45) It is possible that the first mass of reticulocytes appearing after liver therapy may be derived from megaloblasts and may not contain as much porphyrin as those derived from normoblasts and later entering the circulation There was no correlation between the reticulocyte percentage and the erythrocyte protoporphyrin in various other diseases studied Increased amounts of erythrocyte protoporphyrin were regularly

Central Nervous System Complications Arising from Diseases of Blood Forming Tissues Stacy R Mettier (Univ of California) classifies blood diseases which may give rise to symptoms originating in the central nervous system into (1) disease primarily of the central nervous system which is essentially degenerative (2) complications arising from space consuming lesions (3) complications arising from hemorrhagic diathesis and (4) symptoms occurring during the illness which involve the psyche

Addisonian pernicious anemia with subacute combined system disease is an excellent example of group 1 About 75 per cent of patients with pernicious anemia show central nervous system involvement about 40 per cent have involvement of the lateral columns alone and in almost 40 per cent there is combined degeneration of the cord The intensity of the neurologic manifestations may vary markedly depending on mental acuity of the patient severity of the anemia and degree of cord degeneration Among the early manifestations of posterior column involvement may be numbness tingling and feeling of coldness in the extremities Usually these symptoms subside during early treatment thus favoring the hypothesis that they are due to peripheral neuritis However they sometimes persist for years despite adequate liver therapy Late manifestations of posterior column degeneration are a diminished or lost vibratory sense development of ataxic gait and loss of sense of finer co ordination in the fingers Under these circumstances the biceps triceps knee and ankle reflexes will be decreased or absent With lateral column involvement evidences of upper motor neuron degeneration dominate the picture The reflexes are increased there may be ankle clonus the Babinski phenomenon can be elicited and there is spastic paralysis of the lower extremities These lesions and their diagnostic aspect should be well understood so that the patient may be treated not only for the anemia but for prevention of disabilities incident to combined system disease In most cases adequate liver

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but it is more serious Although complete agranulocytosis may not develop in some patients a considerable number show varying degrees of leukopenia Unlike acute hemolytic anemia agranulocytosis results only after the drugs have been given for a considerable period usually one to three weeks it may even develop after discontinuance of therapy Clinically the patient suddenly becomes worse and there may be coincidental development of ulcer in the oral cavity Treatment includes prompt cessation of the drug repeated transfusions liberal fluid intake intensive treatment with liver extract intramuscularly and use of pentnucleotide If the patient has a serious infection and develops a moderate leukopenia from the sulfonamide it is not necessary to discontinue treatment since the chance of severe leukopenia developing may be preferable to withholding a life saving therapeutic agent Furthermore another sulfonamide may be substituted

These drugs are also capable of producing marked thrombocytopenia with resulting hemorrhages of various types and often death All four drugs have been incriminated in 15 such cases in the literature The mortality was high and in the fatal cases suppression of platelet output seems to have been an irreversible process Thrombocytopenia may occur either early or late during treatment and should be considered a possible complication at any time during treatment Obvious treatment is prompt withdrawal of the drug and transfusions

Extreme leukocytosis may occur occasionally the total number of leukocytes reaching 50 000 60 000 or perhaps 100 000 cells per cu mm Sometimes the granulocytes may show an alarming degree of immaturity so that the condition is properly labeled a leukemoid reaction The picture may be confusing to the physician particularly in a patient with clinical improvement because it is difficult to know whether he is becoming better or worse

Sulfonamides should be taken only under close supervision of a physician and adequate hematologic studies should be done in both the early and the late stages

observed four cases of thrombocytopenic purpura complicated by hemorrhage into the central nervous system

Psychotic states in patients with pernicious anemia often develop in the aged when arteriosclerosis and senility may be additional factors contributing to the mental aberration Hyland and Farquharson state that patients with pernicious anemia often show well marked disturbances in the emotional or intellectual spheres or both Emotional upsets include anxiety states with varying degrees of depression and paranoidal trends In contrast to this Mettier observed patients in such a maniacal state that force and isolation were necessary The intellectual defects are manifested by impairment of memory perception and attention With adequate treatment the psychic symptoms are usually lessened or disappear In presence of arteriosclerosis or senility mental symptoms may progress despite treatment

Tropical Eosinophilia Kendall Emerson reports that *this endemic disease apparently widespread in the coastal* regions of southern India is characterized by a chronic paroxysmal cough frequent attacks of asthmatic breathing weakness listlessness loss of weight and appetite and leukocytosis ranging from 20 000 to 60 000 apparently due chiefly to an increase in eosinophils which constitute 50–80 per cent of the total number of white cells Onset is gradual with low grade fever splenic enlargement apathy and weight loss A week later hacking paroxysms of coughing begin usually in the early morning and frequently associated with moderately severe asthmatic attacks resembling true asthma in response to adrenergic drugs There are numerous sibilant and sonorous rales throughout the lungs and prolonged expiration After two or three weeks fever subsides but the remaining symptoms persist and become chronic lasting for years if untreated The disease is benign no deaths having been reported Roentgen appearance of the lungs consists of fine diffuse mot

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therapy results in considerable improvement in the central nervous system symptoms in three to six months

The space consuming lesions include Hodgkin s disease lymphosarcoma myeloma and leukemia (chloroma) and also Gaucher s disease and xanthomatosis Hodgkin s disease and lymphosarcoma are the commonest The neurologic findings are not specific for any one disease and may be protean The symptoms arising from spinal cord compression are of segmental character and vary depending on location and extent of the lymphomatous growth There may be involvement of either motor or sensory tracts and evidences of nerve root compression Extension or metastasis of the lymphomatous process into the cranial vault may be suspected in presence of focal cerebral signs associated with impaired function of the cranial nerve e g with aphasia facial palsy deafness or vertigo Disturbances of vision choking of the disks and stupor indicate progressive increased intracranial pressure Central nervous system involvement is not infrequent in leukemia The lesions may result from leukemic infiltrations or tumor like growths chloroma manifested clinically by cranial nerve palsies signs of pyramidal tract involvement and evidences of meningeal irritation when progressive pressure develops coma may ensue Persistence of severe headache in the frontoparietal or suboccipital regions suggests leukemic infiltration of the meninges

Hemorrhage into the subarachnoid space or within the brain substance may occur early or late in the course of a hemorrhagic diathesis Diseases of the blood forming tissues that are essentially hemorrhagic may result from deficiency in quantity or quality in the elements essential to formation of a satisfactory clot or to a defect in the structure of the vessel wall This group includes therefore arteriosclerosis deficiencies of vitamins C and K hemophilia and other hemorrhagic diseases In thrombocytopenic purpura death usually results from bleeding elsewhere before brain hemorrhage occurs but Mettier

observed four cases of thrombocytopenic purpura complicated by hemorrhage into the central nervous system

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thing with irregular ill defined pea sized areas of increased density scattered thickly throughout lung fields following in general the course of the bronchi and being more numerous in hilar and basal regions generally simulating miliary tuberculosis Etiology is unknown The blood shows no abnormal forms of eosinophils to suggest leukemia and the benign course and absence of clinical signs of periarteritis nodosa make presence of this disease unlikely

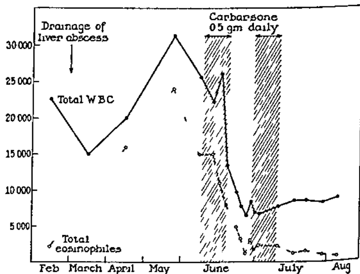


Fig 46—Eff t f ca b d t t l be ot l t g white c ll ph l

Emerson reports a case complicated by liver abscess but which showed the same dramatic response to arsenic administration first reported by Weingarten The patient 30 probably acquired his disease while living in India but it remained latent until resistance had been diminished by a severe intercurrent infection The remarkable therapeutic effect of arsenic points toward a spirochetal or protozoan infection as the etiologic agent The fact that oral treatment is as effective as intravenous suggests that the gastro

intestinal tract may be the chief point of infection although this is not certain since a considerable amount of ingested arsenic may be absorbed

Typical symptoms regressed only briefly after surgery for the liver abscess When diagnosis was finally made 0 25 Gm carbarsone was given twice daily by mouth after a rest period of 10 days a second 10 day course was given There was a slight rise in total white cell count in the middle of the first course of carbarsone without corresponding rise in eosinophils (Fig 46) After the first 10 days there was a sudden drop in white cell count which had been over 20 000 for two months to 9 800 This fall was due almost entirely to decrease of eosinophils in the blood since up to this point they had made up 50 per cent of the total white cell count Thereafter total white cell count leveled off at normal values whereas the level of eosinophils continued to fall to 16 per cent of the total After the second course of arsenic there was a further fall to 9 per cent The chest cleared up on auscultation soon after the first course of arsenic was begun In six weeks he was recommended for limited duty

Blood Typing and Criteria for Blood Typing Serums William Thalhimer (Pub Health Research Inst New York City) states that blood typing tests should be done only with highly titered rapidly acting standardized anti A and anti B typing serums All typing serums should be tested at frequent intervals with known A_1 A_2 and B cells to make certain they have not deteriorated especially if kept in liquid form Bacterial contamination renders a typing serum useless and may even cause nonspecific agglutination serums are therefore safer when kept in frozen or solid state Additional accuracy is obtained by use of two sets of serums in each test and performance of the test by two technicians each using a separate set of serums To check the cell typing plasma or serum should also be tested for its agglutinin content by using both known A_1 and B cells

An accurate standardized method must be used for determining agglutinin level or titer of typing serums This is done by a test tube method of titration Pretrans

(6) I P I t 23 714 7 0 D mb 1943

fusion tests should include direct cross matching of patient and prospective donor s cells and serum or plasma The safety of the universal donor is determined by a simple test A 1 50 dilution of the donor s plasma is made in physiologic saline and a drop of this mixed on a glass slide with a drop of a 2 per cent suspension of the recipient s cells If after mixing and rocking back and forth from time to time for 10 minutes no agglutination is seen with the naked eye the agglutinin titer is not high and the donor s plasma may be used However if the emergency is great the type O individual should be used as donor regardless of the recipient s blood type Direct compatibility tests are practically always carried out by a slide technic A drop of the recipient s plasma or serum is mixed with a drop of a 1 or 2 per cent suspension of the donor s cells on one half of the slide and a drop of the donor s plasma or serum with a drop of a suspension of the recipient s cells on the other half Mixing is done with the two ends of a toothpick the slide is rotated and observed for 10 minutes If time permits the mixtures should be made in separate test tubes with equal parts of the constituents and the test tubes placed in a water bath at 37 5 C for one hour The test tubes are then shaken gently to see if there is visible agglutination if not a drop is placed on a slide and observed under low power Sometimes the serum of very young infants may not contain demonstrable agglutinins corresponding to their blood type If that occurs the blood group of the infant and the prospective donor must be determined with at least one set of potent typing serum and preferably with two sets

Pregnant or recently pregnant women who are Rh negative and need transfusion should receive only compatible Rh negative blood If any person needs repeated transfusions it should be determined whether he is Rh positive or negative If Rh negative then additional transfusions or repeated transfusions are safer if done only with compatible Rh negative blood

TRANSFUSIONS OF BLOOD AND BLOOD SUBSTITUTES

This subject continues to be of military and civilian importance. The search of substitutes for human plasma continues especially since after the war blood may not be as freely donated as it now is for the use of the armed forces—Eds

Red Cell Reinfusion and Frequency of Plasma Donations This study by Co Tui F C Bartter A M Wright and R B Holt was based on the assumption that reinfusion of red cells would relieve donors of 80 per cent of the protein drain and enable them to donate plasma oftener than at the now prevailing intervals of eight weeks Six healthy volunteer donors were studied each receiving back the red cells suspended in 5 per cent dextrose solution the day after bleeding [Red cells should never be suspended in glucose solution alone for if warmed the glucose will penetrate and cause hemolysis unless sufficient plasma or salt *is present to maintain external osmotic pressure* — Eds] In the first group one gave three donations and two gave four each on alternate days The total amount bled was *approximately 34 per cent of the blood volume* calculated from body weight In the second group each gave a full sized donation weekly one for 9 weeks and two for 12 weeks In all the total plasma protein and hematocrit returned to normal within 48 hours after reinfusion of the red blood cells The final hematocrit hemoglobin and plasma protein values were practically the same as the initial values Bilirubin levels and reticulocyte counts were normal in all donors throughout the study the final red cell fragility tests were also normal

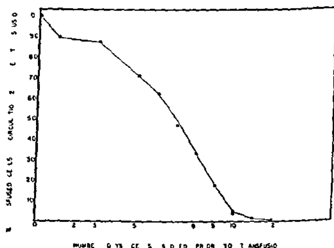
On the basis of this preliminary work the authors recommend the practice of red cell reinfusion into donors derived from a malnourished population or when a large proportion of donors are women Pyrogenic reactions to reinfusions may be avoided by using nonpyrogenic fluids

(7) J A M A 124 331 336 Feb 5 1944

or pyrogen retentive filters An increase in frequency of donations per donor would materially aid the program.

Effect of Storage of Citrated Blood on Survival of Transfused Erythrocytes Joseph I Ross and Milan A Chapin* (Boston Univ) point out that the survival in vivo of transfused erythrocytes and the effectiveness of blood preservatives in prolonging such survival can readily be determined by use of donor red blood cells labeled with radioactive iron They used this method in study of the effect of storing citrated blood on survival of erythrocytes

Citrated blood derived from donors with hypochromic



F g 47 — Effect of t ag ot t t d blood on su v l f tran fused yth ocyt s

anemia who had received radioactive iron was stored in a refrigerator for periods varying from 1 to 14 days Healthy adults were given intravenous injections of 40 or 50 cc aliquots of the labeled blood and their blood was examined at varying intervals after transfusion Solutions of Evans blue dye were injected immediately prior to transfusion for subsequent determination of plasma volume by the method

(8) J A M A 1 3 82 8 9 N v 27 1943

of Gibson and Evelyn The total radioactivity in circulation at the time each sample was withdrawn was calculated from the formula Total radioactivity in circulation = radioactivity per cc blood × total blood volume The percentage of the total transfused radioactively tagged cells in circulation at any given time was calculated from the formula Percentage of transfused radioactivity in circulation = total radioactivity in circulation — total radioactivity of the transfused blood

Storage of citrated blood was found to exert a deleterious effect on erythrocytes (Fig 47) When stored for 6 days only 50 per cent of the erythrocytes survived and when storage lasted 10 days less than 10 per cent of cells survived for 24 hours

The determination of erythrocyte radioactive iron concentration at varying intervals after transfusion revealed that after an initial decrease for about 24 hours the concentration of radioactive iron began to increase in each individual studied It was concluded that the rapid decrease represented destruction of transfused cells and the subsequent progressive increase a re utilization of the labeled iron originally contained in these cells This labeled iron seems to be used for synthesis of hemoglobin preferentially to and more rapidly than plasma iron

Survival of Preserved Red Cells after Transfusion. O F Denstedt Dorothy E Osborne H Stansfield and I Rochlin (McGill Univ) compared the merits of two preservative mixtures by storing blood at 4 C for various periods up to 57 days and following red cell survival after transfusion One solution was a modification of DeGowin s citrate dextrose formula 400 cc blood 80 cc citrate (3 2 per cent) and 120 cc dextrose (5 4 per cent) This gave a ratio of blood to isotonic diluent of 1 ½ a proportion giving optimal preservation with most bloods The other solution was a buffered citrate dextrose mixture The phosphate buffer was prepared as follows 0 3 molar (4 14 per cent) monobasic sodium phosphate 1 000 cc 0 3 molar

(9) A tb l gy 5 37 5 M 1944

(1 2 per cent) sodium hydroxide 925 cc water 480 cc This mixture is isotonic with physiologic saline solution and has a pH of 7 4 Blood and diluent were mixed thus 400 cc blood 60 cc citrate 60 cc buffer and 80 cc dextrose Fresh twice distilled water was used in the solutions Thus both solutions were isotonic with normal plasma and were used with blood in the proportion of 1 volume of the latter to ½ volume of diluent Under these conditions red cells can be stored for six weeks and in some instances two months with less than 1 per cent hemolysis The buffered solution tends to prevent dense packing and cohesion of cells during sedimentation and is more effective than the unbuffered mixture in retarding autolytic changes particularly the breakdown of organic phosphates during storage

Thirty five transfusions were done and cell survival was followed by the method of Wiener Despite the merits of the buffered mixture red cell survival was not noticeably superior to that obtained with the unbuffered solution With either mixture red cells stored up to 18 days survive as well as fresh cells after transfusion and may be detected in the circulation for about 125 days Samples stored for 24 days undergo slightly more rapid elimination, but in several instances the cells did not disappear completely until about 125 days Beyond 24 days storage cell destruction after transfusion is still more rapid and the maximal survival time is decreased There is evidence that cells are not necessarily destroyed as soon as they disappear from the circulation but that a considerable number may reappear later usually between the fifteenth and the twenty fifth day and sometimes about the sixtieth day after transfusion Even with 30 day old blood cell survival is sufficiently good during the first week after transfusion to warrant using such samples in emergencies

Caution against Too Liberal Use of Citrated Blood in Transfusions, based on experimental results is given by Jacques Bruneau and Evarts A Graham[1] (Washington

(1) A h S g 47 319 325 October 1943

Lnn) Two groups of dogs were bled repeatedly of 1 per cent of their body weight and the blood was reinjected con tinually sodium citrate in 0 6 per cent concentration being used as an anticoagulant in group A and heparin in group B Average survival period in group B was almost three times that in group A Five animals in group A developed dyspnea and convulsions or fibrillary twitchings prior to death in none of the animals in group B were convulsions or fibrillary twitchings noted The blood pressure in group A fell to a low level 2[1] hours prior to death whereas no such drop occurred in group B In group A the clotting time showed a constant decrease during the first hour and an increase in some animals before death In group B no initial decrease was noted and all animals showed marked increase in clotting time toward the end The serum cal cium in group A was definitely increased prior to death in the four dogs studied no changes in initial and terminal serum calcium values occurred in group B

The earlier deaths of animals in group A should be ascribed to the toxic action of large amounts of sodium citrate possibly through alteration in the degree of calcium ionization in the circulating blood

Studies on Transmissibility of Malaria by Plasma Transfusions Eugene I Lozner and Lloyd R Newhouser (U S Naval Med Sch ol Bethesda Md) report re sults of administration of plasma prepared from donors with active malaria and preserved by different technics to 35 patients with general paresis or nervous system dis eases amenable to malaria therapy Dosages ranged from 60 to 270 ml No immediate untoward reactions occurred In 20 administrations of thawed plasma which had been shell frozen in a solid carbon dioxide alcohol bath and in 3 administrations of restored plasma which had been dried from the frozen state no transmission occurred In two administrations of plasma preserved in the liquid state at room temperature for one day before injection there was one definite and one probable transmission In five

( ) Am J M S 06 141 146 A gu t 1943

administrations of plasma preserved in the liquid state for one week no transmission was observed except in one doubtful case In five administrations of plasma preserved in the liquid state for two weeks no transmission was observed

These results indicate that the danger of transmission of malaria by plasma is minimal The only definite transmission was caused by liquid plasma 1 day old In the two doubtful cases the patients had had malaria previously Since plasma under 10 days old is rarely administered for bacteriologic reasons liquid plasma over 1 week old and frozen and dried plasma are safe as regards malaria transmissibility The authors assume that in reported cases of transmission of malaria through stored whole blood the chief vector was the parasitized red cell

Concentrated Red Cell Transfusions Monte L Binder and Arthur Klein (Med College of Virginia) describe a procedure for preparation of CRC (concentrated red cells) its use is as efficacious as whole blood in raising the hemoglobin level and produces no deleterious effects

PROCEDURE —The concentrated red cell preparations were obtained from regular hospital donors The Fenwal apparatus a semiclosed system was used to collect 500 cc blood in 0 cc of per cent sodium citrate solution The blood was typed by the open slide microscopic method and then stored at 4 to 6 C The red cells were usually prepared for use as the need for them arose When obtainable the blood of the patient s own group was used otherwise group O was used The blood selected was 2 to 7 days old Before preparation the donor s blood was cross matched with that of the recipient by the test tube method of Land teiner If more than one donor s blood was to be used each donor blood was cross matched with that of the recipient and also with the other donor blood Under sterile precautions the plasma was aspirated off into a pooling flask the pipet was then inserted to the bottom of the bottle and the red cells were aspirated into a different bottle leaving the buffy coat or gel which is composed of leukocytes platelets and fibrin All cells to be used in the same transfusion were aspirated into the same

(3) Am J M Sc 08 95 103 J ly 1944

bottle The cells obtained from one donor blood in this way were called 1 donor unit of concentrated red cells i e 1 donor unit of CRC After preparation the CRC were either used immediately or returned to the refrigerator until used. They were never kept longer than two days after preparation

The CRC were given in the regular Upjohn recipient sets which were equipped with metal screen filters Dilution to maintain flow was unnecessary The reservoir of blood was elevated about three feet higher than the usual level of three feet above the antecubital fo n to btain more pressure Average time of administration for each unit of CRC was 30 minutes A fairly typical donor unit consisted of 225 cc in volume with 21 9 Gm per 100 cc hemoglobin and 71 3 per cent hematocrit all hemoglobin determinations were done by the Sahli method and all hematocrits in Wintrobe tubes

There were 11 reactions in 124 transfusions 9 consisted of chills and fever 1 was allergic (urticaria) and 1 was a *hemolytic reaction two days after transfusion* Five of the 11 reactions occurred in 20 transfusions given to two patients who received CRC primarily because they reacted to most whole blood transfusions despite all attempts to find a source of incompatibility Discounting these two there were six among 104 transfusions or a total reaction rate of 5 8 per cent In the first 3 000 whole blood transfusions given through the authors blood bank the total reaction rate was 7 8 per cent Aside from this lower percentage with CRC the reactions were also milder In the two patients who received the 20 transfusions the chills were not as severe or as prolonged and temperature elevation was less marked

CRC transfusions cannot be used for patients with acute *blood loss until the blood volume has returned to normal* and the only deficit is in hemoglobin Their use is contraindicated in shock burns and when the plasma proteins are below normal The uses of CRC are not limited merely to elevating the hemoglobin level Evans has reported that CRC were apparently as efficacious as whole blood in controlling bleeding and other purpuric symptoms of blood dyscrasias The authors observed the same beneficial results in a girl 12 with a diagnosis of monocytic leukemia

Despeciated Bovine Serum (D B S) Substitute for Human Plasma F Ronald Edwards (Univ of Liverpool) states that substitutes for human plasma hitherto have not fulfilled the three criteria retention in circulation and eventual metabolism exertion of equivalent osmotic pressure nontoxicity nonantigenicity and freedom from antibodies Bovine serum can be made safe for man and appears to meet these three criteria

Clinical trials of D B S in 26 cases indicate that its administration is unassociated with severe reactions No rigors were observed or serum sickness and delayed reactions even with large quantities Slight fever was noted in some patients but never over 100 F No clinical evidence of intravascular hemolysis or hemoglobinuria was observed Protein was never found in the urine if it had previously been absent No marked increase of protein occurred in patients who had preinfusion albuminuria suggesting that the protein does not pass through the renal capillaries and there has been no evidence that it passed out of any other capillaries in the body Osmotic pressure effects are difficult to assess but the result in one case of hypoproteinemia with edema suggests that this is considerable In cases of acute empyema with large and rapid protein loss administration of D B S was marked by immediate feeling of well being Anaphylaxis was not encountered when tested for in 10 patients

The solution is easily prepared is available in enormous quantities is completely stable and can be stored at room temperature It may be given rapidly and in large amount and no patient seems to have been adversely affected Final judgment must await the results of more detailed hematologic and biochemical studies of the effect of its administration in the state of shock hypoproteinemia and protein deprivation and loss

Technic—Blood is collected at the abattoir in sterile vessels from 16 to 20 pt is obtained from each animal The blood is allowed to form a firm clot After three days the serum is

(4) B M J 1 73 6 Jan 15 1944

drained off into Winchesters and passed through wood pulp to remove remaining erythrocyte A small sample is tested for gel formation by adding a few cubic centimeters of serum to the appropriate amount of formalin and ammonia and immersing in a water bath at 75 C

Serum is passed through a double Seitz filter if gelatification occurred in the sample saline dilution is necessary first Filtered serum is collected in units of 400 cc in standard transfusion bottles with perforated screw top and rubber diaphragms Requisite formalin and ammonia are added by injection through the cap 0 2 per cent by volume of formaldehyde shake then 0 2 per cent by volume of 0 88 per cent ammonia *Any excess formaldehyde is converted by the ammonia* into hexamine which is innocuous Sterility tests are then made. The bottles are placed in a water bath at 60 C to prevent cracking of glass and temperature is raised rapidly to 75 C and maintained for 30 minutes during which time the serum is heated to about 73 C On cooling the serum is ready for use

Clinical Use of Isinglass H E Pugsley and R F Farquharson report on intravenous administration of purified powdered isinglass to 61 patients at the Toronto General Hospital The powder dissolved in physiologic saline solution and autoclaved was stored in the refrigerator until used the longest period of storage being 19 days Concentrations of 4 6 or 7 per cent were used

Fifty eight administrations were given to 51 patients chiefly for the purpose of detecting pyrogenic reactions or other toxic effects Doses varied from 25 to 800 cc average 300 cc the solution was infused by the gravity drip method except for the 25 cc doses which were given by syringe Febrile reaction was noted in eight instances In no case was fever sustained longer than a few hours and the highest elevation of temperature 103 8 F per rectum occurred in a patient who had slight fever before the injection Two patients complained of initial chill the others of a chilly sensation Other associated symptoms were malaise headache and nausea Results of intradermal skin tests with isinglass solution were negative in the two patients tested No other reactions occurred

(5) C M A J 9 6 274 Octobe 1943

Ten patients with shock or severe circulatory collapse were treated by intravenous administration of isinglass without toxic manifestation The dose varied from 200 cc in an infant to a total of 8 800 cc in three days to a patient with severe burn shock Of three patients with acute hemorrhage two required additional blood transfusions to bring blood pressure to normal in one blood pressure returned to normal after administration of isinglass Three patient with shock following extensive burns an infant and two adults responded favorably in one who later died of toxemia the serum proteins were normal at time of death. Two patients with shock following compound fractures were benefited Improvement resulted in two patients with severe circulatory collapse but both died subsequently

Five Cases of Jaundice Following Transfusion of Whole Blood or Human Plasma are reported by R E Steiner The patients were battle casualties from North

Case	Age	Transfusion			Onset of Symptoms	Interval in Days	Recovery
		Date	Blood Cc.	Plasma Cc			
1	23	4/ 7	500	2 500	7 /3	87	7/26
2	28	4/11		3 000	7/18	98	8/16
3	21	5/ 9	1 000		8/31	114	9/23 Still faint trace of jaundice
4	36	3/21	500		7/10	111[1]	8/ 3
		3/23	500				
		3/24	500	250			
		3/29	1,200				
		4/14	850				
5	24	3/22	500		5/27	66	died 5/29

Africa and were admitted two to three months after being wounded they then developed jaundice All had had transfusions of whole blood human plasma or both in varying quantities Treatment in every case was primarily some form of surgery with chemotherapeutic measures such as

(6) P t M J 1 110 111 J n. 22 1944

antisyphilitic and anti gas gangrene serum and massive doses of sulfonamides Data on the cases are shown in the table

The clinical picture resembled catarrhal jaundice or infective hepatitis in many ways The patients were slightly febrile with nausea anorexia slight abdominal discomfort vomiting and signs of jaundice liver enlargement and tenderness in the right subcostal region In three cases there was definite lack of free bile in the urine with an excessive amount of urobilin In three cases there was marked mononucleosis Some etiologic significance must be attributed to (1) the temporal coincidence of the transfusions within about three months in four cases and (2) the fact that jaundice has been observed only in casualties from North Africa and not in those from other war theaters It would appear therefore that while transfusion may be the cause of the jaundice certain special circumstances must be attendant on the transfusion before jaundice is produced

Viscose Tubing for Transfusions Henry Naftulin A M Wolf and S O Levinson (Michael Reese Hosp Chicago) believe that incomplete cleansing of rubber tubing owing to the residual protein left in its lumen is a major cause of pyrogenic transfusion reactions Too drastic cleansing of rubber eventually destroys its original elasticity thus reducing its desirability for intravenous administrations As a rubber substitute the heavy walled viscose tubing is much sturdier than the regular viscose tubing described by Hartman The material is impregnated with glycerin which acts as a hygroscopic agent When moist the tubing is quite pliable Viscose tubing is supplied in lengths of 1 500 ft on spools its low cost is conducive to its one time use Vaporization of moisture during sterilization may be inhibited by placing the desired length of viscose tubing as a compact package in a glass tube Refrigerator storage is advisable for partially used rolls Experiments have proved the heavy walled viscose tubing

(7) J A M A 133 1 4 Oct 9 1943

to be pyrogen free and impermeable to pyrogens and bacteria In 1 137 blood transfusions given through visco e tubing the incidence of pyrogenic reactions was 0 64 per cent a material decrease from the reaction rate occurrin with rubber tubing

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HEMOLYTIC ANEMIAS

A number of articles discuss various aspects of the problems of increased blood destruction in hemolytic anemias —Eds

Acquired Hemolytic Anemia V R Ma on (MC AUS) reviews the literature and reports 12 cases of acute subacute and chronic acquired hemolytic anemia of unknown etiology

In children the acute form usually begins abruptly with chills and fever and frequently runs its course in a week or 10 day In adults there is a variable period marked by increasing fatigue weakness and malaise In a few ca es this period is brief but in most it is insidious lasting a few weeks or even months before a physician is consulted The complaints are exhaustion dizziness anorexia nausea and often abdominal cramps Some complain also of head ache breathlessness and faintness on exertion Pallor and jaundice are observed first later the symptoms rapidly become more severe and include high temperature chills profound anemia and at times delirium or convulsions Splenomegaly is constant One of Mason s patients pre sented an erythematous lesion of the skin The stools are often dark because of large amounts of bile pigment and the urine contains large amounts of bile and urobilinogen In some patients especially children after a variable num ber of transfusions the symptoms improve and complete recovery follows In others transfusions produce intensifi cation of the icterus and fever without gain in hemo globin in some reactions to transfusion occur In some instances the patient s condition soon becomes critical and splenectomy is necessary as a life saving measure Dura

(8) A ch I t Med 72 471 493 Oct b r 1943

tion of the acute type varies There are a fulminating type especially in children and a subacute type lasting one to three months A number of cases are of the chronic type marked by acute hemolytic crises and by instability of the hemolytic balance of red cells but otherwise presenting the same hematologic features as the acute type

The characteristic blood picture consists of profound anemia with numerous macrocytes and spherocytes a color index at or above unity marked reticulocytosis with other evidences of immaturity of the macrocytes numerous normoblasts and leukocytosis This type of morphologic alteration of red cells was called pseudomacrocytosis by *Dameshek and Schwartz* *An infrequent hematologic phe* nomenon in acute hemolytic anemia is the presence of an auto or iso agglutinin and in some cases of an iso and/or autohemolysin In Mason s cases auto or iso hemolysis was not present An auto and/or iso agglutinin was present in four cases Resi tance of red cells to hypo tonic saline solutions was normal in most of the reported cases In several instances fragility of the red cells was greatly increased but in most of Mason s cases was nor mal In one patient hemolysis of red cells with hypotonic saline began at 0 85 per cent and was complete at 0 26 per cent in another the corresponding figures were 0 82 and 0 28 in a third 0 8 and 0 26 and in a fourth 0 84 and 0 34 In the author s and in the reported cases the osmotic fragility of red cells degree of spheroidicity and presence of auto or iso-antibodies in the serum in vitro did not correlate with the degree of anemia or the rapidity of its development Hemoglobinuria was not present in any of Mason s patients or in patients observed by Dameshek It was reported in 30 per cent of cases of the more ful minating type in children

Pathologic changes described were moderate enlarge ment of the spleen with packing of the splenic pulp with red cells to such a degree that the normal venous sinuses were obliterated hyaline thrombi in the radicles of the splenic vein or small peripheral venules marked hyper

plasia of the bone marrow hemosiderosis of the spleen and liver and some degree of erythrophagocytosis in both these organs and usually marked hyperplasia of reticulo endothelial cells in the spleen liver and bone marrow

The disease may heal spontaneously or it may be cured by transfusion or splenectomy The more chronic types of the disease may or may not be cured by splenectomy During the serious hemolytic crisis splenectomy may be life saving even if it does not lead to complete cure Some patients with the chronic type die of anemia or intercurrent disease and some of a combination of anemia and hepatic insufficiency with marked fibrosis of the liver The latter patients have pigment stones in the gallbladder common duct and hepatic ducts and frequently small putty like pigment stones in the intrahepatic biliary ducts

[The following articles are concerned with the theoretical and clinical aspects of the Rh factor —Eds]

Heredity of Rh Blood Types Alexander S Wiener Eve B Sonn and Ruth B Belkin (New York City) report that with the aid of three varieties of anti Rh agglutinins five sorts of Rh agglutinogens can be demonstrated which in combination determine eight types of human blood To account for these variants of the Rh agglutinogen Wiener proposed a theory of six allelic genes This theory postulates the existence of a series of allelic genes Rh_1 Rh Rh Rh Rh and rh named after the serologic properties which they determine The gene rh is recessive to the other and in homozygous individuals gives rise to the Rh negative type The gene Rh determines an agglutinogen Rh which reacts with anti Rh_1 but not with anti Rh or anti Rh agglutinins Similarly the agglutinogen determined by the gene Rh reacts only with the anti Rh agglutinin while agglutinogen Rh reacts only with the standard anti Rh agglutinin but not with anti Rh_1 or anti Rh The agglutinogens which are determined by the genes Rh_1 and Rh on the other hand are characterized by their ability to react with two of the three primary Rh agglutinins For

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example agglutinogen Rh_1 reacts with agglutinins anti Rh_1 and anti Rh but not with agglutinin anti Rh_2 However the fact that blood of types Rh_1 and Rh each react with two distinct agglutinins does not mean that such bloods contain two genetically separate corresponding properties These agglutinogens are assumed to be due to the action of single genes and are therefore inherited as a unit their serologic properties being ascribed to the presence of two or more partial antigens within the molecule The behavior of Rh_1 and Rh_2 bloods is therefore comparable to the reactions of blood of subgroup A_1 with serums anti A and anti A_1 Since every individual has two genes of every allelic series one derived from each parent they must also have a pair of Rh genes Accordingly 21 genotypes are theoretically possible under the six gene theory and if the phenotype corresponding to each genotype is assumed to represent merely the combined effect of the two genes then the 21 genotypes give rise to 8 phenotypes When considering the reactions of each type of blood with the serums anti Rh and anti Rh designated secondary serums to indicate that they each contain two of the three primary agglutinins it is found that serums anti Rh and anti Rh differ from the standard anti Rh only in their reactions with bloods of the rarest types Rh and Rh The fact that the most common human antiserums are anti Rh anti Rh and anti Rh coupled with the difficulty that most of the serums available are weak and therefore give irregular results accounts for the confusion that has been caused by the discrepancies between the reactions of these serums

Results of an investigation of the Rh blood types in 97 families with 275 children and in 135 mother child combinations were in complete agreement with the theory of the six allelic genes When the theory was tested by applying the chi square and gene frequency methods to data on the distribution of the Rh types in the population the agreement was also satisfactory

Aside from their theoretical significance the Rh blood

plasia of the bone marrow hemosiderosis of the spleen and liver and some degree of erythrophagocytosis in both these organs and usually marked hyperplasia of reticulo-endothelial cells in the spleen liver and bone marrow

The disease may heal spontaneously or it may be cured by transfusion or splenectomy The more chronic types of the disease may or may not be cured by splenectomy During the serious hemolytic crisis splenectomy may be life saving even if it does not lead to complete cure Some patients with the chronic type die of anemia or intercurrent disease and some of a combination of anemia and hepatic insufficiency with marked fibrosis of the liver The latter patients have pigment stones in the gallbladder common duct and hepatic ducts and frequently small putty like pigment stones in the intrahepatic biliary ducts

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(4) J Exper Med 79 235 53 March 1944

this will determine the Rh antigens to which the mother is sensitive either a specific hapten or a polyvalent mixture of haptens might be used in such cases Similarly from the Rh type of the husband or child the quality of the Rh agglutinins present in the sensitized mother s serum might be predicted Thus time would be saved in standardizing new antiserums obtained from mothers of erythroblastotic babies

The authors believe that their findings justify the mediocolegal application of the Rh tests in cases of dis puted parentage The striking differences in distribution of the Rh blood types in different races may find practical application in anthropol gy To the geneticist the Rh blood types are of interest because they furnish another striking example of mendelian inheritance in man and these properties serve to mark another pair of chromosomes for linkage studies

Role of Subtypes of Rh in Hemolytic Transfusion Reactions and Erythroblastosis Alexander S Wiener (Jewish Hosp Brooklyn) points out the analogous prob lems of hemolytic reactions to repeated transfusions and transfusions to erythroblastotic infants and their mothers The Rh factor is the antigen involved in about 90 per cent of cases

A case of icterus gravis in an Rh positive infant with Rh positive parents was explained by demonstration of anti Rh iso antibodies in the maternal serum This appar ently paradoxical result was clarified after further tests for Rh subtypes when it was found that the mother be *longed to subtype Rh father and infant to subtype* Rh_1 Rh Despite the apparently minor difference in reactions of the bloods of mother and infant and the weakness of the anti Rh iso antibodies in the maternal serum the disease in the infant was fulminating Recovery followed transfusions of the mother s washed blood cells suspended in the father s plasma In hemolytic disease of the new born the mother s washed cells are always suitable for

(5) Am J Cl P th 14 5 60 J ry 1944

types are important in relation to the application of the Rh test in clinical medicine They explain the puzzling differences in the human Rh antiserums For routine diagnostic work the standard anti Rh serums giving 85 per cent positive reactions are to be preferred because such serums react with about equal intensity with bloods of types Rh_1 and Rh_2 With such serums the bloods of persons belonging to the rare types Rh and Rh would not react which is advantageous because individuals of type Rh and probably also Rh can be sensitized to the factor Rh In such cases transfusion with Rh negative blood is as reasonable as use of group O blood for individuals with blood type A B and AB in ordinary cases in which intra group sensitization does not exist For classifying blood donors the standard anti Rh serums are not quite as satisfactory because an Rh negative individual sensitized to the factor Rh_1 for example might have a hemolytic reaction if given type Rh blood

The diagnostic human anti Rh serums most commonly available are not the standard anti Rh but anti Rh serums Such serums frequently have the failing that they react less intensely with bloods of type Rh than with blood of type Rh_1 because the standard anti Rh agglutinin which they contain is considerably weaker than the anti Rh agglutinin If they are used controls of Rh positive blood of type Rh as well as blood of type Rh_1 must be included and if necessary the reactions may be accentuated with the aid of brief centrifugation

Determination of the Rh type of the father of an erythroblastotic baby permits a more definite statement as to prognosis of future pregnancies If the father belongs to type Rh_1Rh all children must be Rh positive half Rh_1 and half Rh_- (usually) so that the prospect of the sensitized mother bearing normal infants with this father is extremely remote Furthermore if it should become feasible to develop a method of preventing the disease by injecting Rh haptens into the mother or fetus then it might be important to know the Rh type of since

Rh blood group is most commonly involved in its causation other red cell antigens may behave similarly While in 1 pregnancy in 10 the mother is Rh negative and the baby Rh positive and in 1 pregnancy in 5 the mother has an agglutinin for an antigen of the A B O system of groups present in her fetus the incidence of the disease is much less than is apparently possible R R Race G L Taylor D F Cappell and Marjory N McFarlane studied 50 families in which erythroblastosis foetalis had been diagnosed

Of the 50 mothers 6 were Rh positive and 44 Rh negative the serums of 38 of the Rh negative women contained anti Rh agglutinins Despite absence of demonstrable anti Rh agglutinins in the other Rh negative cases it is highly probable that iso immunization of the mother to the Rh factor played a part In some of them the absence of anti Rh agglutinins may have been due to length of time since delivery which averaged four years against less than a year for the other 38 In none of the six was there any certain evidence of other blood group factors being involved Examination of offspring of these 44 Rh negative mothers 33 healthy and 16 affected children failed to show one Rh negative child The absence of Rh negative children from the healthy group is highly significant and may be provisionally explained by two circumstances both in favor of the predominance among those showing the condition of families in which the fathers are homozygous (1) not all Rh positive children of Rh negative mothers are equally liable to the disease and (2) ascertainment is more frequent when the affected child has an affected sibling than when it is the only one affected in the family

In the present series no mother who once had an erythroblastotic infant ever had a normal surviving child with one exception This child is the fourth in the family and is Rh positive with certain serums Of the first children borne by the 44 Rh negative mothers 38 were unaffected 5 were stillborn and 1 is known to have had

(6) Brit M J 89 9 Sept 4 1943

transfusion and Rh negative blood is almost always suitable even though mother and infant are both Rh positive excluding cases of course in which iso-antibodies of specificity different from anti Rh are demonstrable in the maternal serum

In patients with unexplained hemolytic reactions to repeated transfusions it is worth while to try a transfusion or biologic test with 50 cc Rh negative blood even though the patient is Rh positive before the reactions are ascribed to a factor other than Rh unless immune iso antibodies of a specificity different from Rh are demonstrable in the *patient's serum In general in such cases use of Rh* negative donors is comparable to use of group O individuals as universal donors for ordinary transfusions

Existence of subtypes of Rh in human blood accounts for the difference in specificities among human anti Rh serums in contrast to the uniformity of animal immune antirhesus serums all of which give parallel reactions This indicates that the red cell antigens responsible for the reaction are identical in all rhesus monkeys and that differences comparable to the human subtypes of Rh do not exist in this species

The apparently puzzling specificities of different human anti Rh serums can be explained if the Rh subtype of the blood donor is determined in cases of hemolytic transfusion reactions or the subtype of the husband and/or children when serums are obtained from mothers of erythroblastotic infants Tests in cases of erythroblastosis disclosed no case in which agglutinins were found in the serums of the mothers that could not be accounted for by the Rh type of the husband or infant

Wiener reports a case of hemolytic disease of a newborn in which hemolysis was caused principally by Rh iso-antibodies acquired by the infant through ingestion of maternal milk

Rh Factor and Erythroblastosis Foetalis Recent American work has shown that iso immunization is important in the etiology of erythroblastosis foetalis Although the

of homozygotes among the fathers of erythroblastotic children should be indicated by the proportion found to be St negative

G L Taylor and R K Race (Cambridge Univ) further examined 46 families in which the disease occurred and in which all the mothers were Rh negative and had anti Rh agglutinins in their serums 18 of the fathers were St negative and 28 St positive The study indicates that there is a marked preponderance of homozygous fathers in families affected by hemolytic disease of the new born the homozygote appears to be about four or five times more dangerous than the heterozygote This predominance of homozygotes affects enormously the chances of Rh negative and therefore unaffected children being born The genotype of about three fourths of Rh positive persons can be determined serologically and unless it can be shown that the father is heterozygous in this way or by his having an Rh negative child or an Rh negative parent the prognosis is unfavorable

Hemolytic Disease of the New Born (Erythroblastosis Foetalis) Its Treatment with Rhesus Negative Blood Janet D Gimson reviews a series of 19 consecutive cases of hemolytic disease of the new born collected from March 1942 to February 1943 at the Hospital for Sick Children Great Ormond Street Seventeen were primarily cases of icterus with or without anemia two were of anemia only without jaundice Two patients had transient edema of the eyelids one had ascites in addition to jaundice and pallor One appeared mentally defective Age at admission varied from three days to six weeks Three were first borns seven had no pertinent family history The classic family history in five cases included siblings born jaundiced and dying soon after birth or surviving in some instances only to be mentally defective or kernicteric or of still births and miscarriages In four it included what might be called physiologically jaundiced infants All the mothers

(7) Brit M J 1 288 89 Feb 6 1944
(8) Ibid 93 97 Sept 4 1943

erythroblastosis Although anti Rh agglutinin was not found in the mother s serum in this last case, it is likely that this factor was responsible for the baby was O Rh positive therefore it does not seem possible that the A B O system was involved After the second birth, there was a steadily increasing proportion of affected children

On the other hand the first children born to four of the six Rh positive mothers had erythroblastosis foetalis The earlier onset in this group might be due if the A B O system of groups was responsible to the iso agglutinin being already present in the mother s serum In the 50 families investigated about one fourth of the children diagnosed as affected survived three fourths were born dead or died usually in the first week Sex ratio of the affected children was about equal

Hemolytic Disease of the New Born. A predominance of homozygous RhRh fathers in families where an Rh negative mother has borne children with hemolytic disease of the new born has been suggested by Race Taylor Cappell and McFarlane [preceding article] An Rh negative mother is more liable to be immunized when every pregnancy is Rh positive and provides the antigenic stimulus as it does with a homozygous husband than when he is heterozygous Rhrh and some of the children are positive and others negative This being so obviously the proportion of homozygous fathers producing affected children will be greater than that of heterozygous fathers In a random sample of Rh positive males about three of seven must be homozygous and four must be heterozygous Race and Taylor have described a serum which discloses the genotype of half the persons who are homozygous RhRh This serum called St agglutinates the blood of all Rh negative rhrh and of all heterozygous Rhrh persons but it fails to react with about 20 per cent of bloods (St negative) all of which must therefore be homozygous RhRh and represent about half the Rh positive homozygotes about 38 per cent of the population Race and Taylor pointed out that the extent of any preponderance

A transfusion rate of 15–20 cc an hour was maintained

Sixteen patients are apparently normal Three died elsewhere after being dismissed with a normal blood picture One died of bronchopneumonia two whose mothers serum had exceptionally high titer antibodies died of probable brain damage

Gimson makes several recommendations (1) Blood transfusions of Rh negative blood free of agglutinins should be given in hemolytic disease of the new born The general condition of the infant will rapidly improve in some instances a 24 hour stay at the hospital suffices and a minimal number of transfusions is necessary (2) A store of Rh negative blood should be available at pediatric and maternity hospitals (3) Pregnant women who have previously delivered an infant with hemolytic disease should be tested for the Rh factor (4) An infant born jaundiced with a strong family history of hemolytic jaundice should immediately be given a transfusion of Rh negative blood regardless of erythrocyte and hemoglobin levels

[The next two articles show that the anti Rh agglutinins may be present in the maternal circulation but may or may not penetrate freely into the circulation of the fetus —Eds]

Rh Antibodies in Maternal Circulation without Clinical Manifestations of Erythroblastosis in Child Gerald C Dockeray and Hans Sachs (Trinity College Dublin) observed four mothers whose serum contained marked amounts of anti Rh agglutinins but who did not give birth to infants exhibiting clinically demonstrable manifestations of erythroblastosis foetalis Thus apparently Rh antibodies may be found in the mother without erythroblastosis occurring in the child It would therefore be profitable to examine the serums of pregnant women at random for presence of Rh antibodies regardless of whether their histories suggest the possibility of development of erythroblastosis in the baby One case particularly supports this conclusion A primigravida in the thirty eighth week of pregnancy belonged to group O and her blood was Rh negative

(9) J Imm l 48 41 46 Ap l 1944

of these 19 infants were Rh negative and all the infants were Rh positive Anti Rh agglutinins were found in the serum of all but one mother The serologic findings are of diagnostic assistance since in some mild cases it is impossible to state whether only physiologic jaundice is present Congenital obliteration of the bile ducts had to be considered in two cases in these also blood findings aided in diagnosis

Transfusion was considered necessary only when the erythrocyte count was below 3 500 000 for this reason it was not done in one case In the others the procedure was varied as experience accumulated Rh positive blood was given in the first three cases and there was evidence of continued or even increased hemolysis and jaundice The next transfusion was of Rh negative blood on the theory that since the fetal blood is Rh positive and undergoing destruction it is desirable to give blood which is not so rapidly destroyed although further hemolysis of the red cells is not prevented In a few cases mixed transfusions of Rh positive and Rh negative blood were given Rh negative erythrocytes survived at least 90 days whereas Rh positive erythrocytes were often destroyed in a few days after transfusion Because of these findings the later patients in the series received Rh negative blood only No increase of jaundice was noted and no more than two transfusions were needed Only one reaction occurred in a patient who received a mixed transfusion of Rh positive and Rh negative blood Two Rh negative blood transfusions were given subsequently without reaction

The transfusions in the present series were larger than usually given the volume in cubic centimeters being calculated from the formula

$$\frac{\text{\% rise in hemoglobin required}}{100} \times \text{blood volume}$$

The blood volume was computed as approximately 88 cc per kg body weight calculated on expected weight for age from birth weight All transfusions were given by drip method into the internal saphenous or cubital fossa vein

marked polychromatophilia and achromia moderate anisocytosis and poikilocytosis 321 normoblasts and 27 megaloblasts per 100 white cells Transfusion of 100 cc blood from an Rh negative male donor was given into the anterior fontanel Intramedullary transfusions were unsuccessful probably due to marrow hyperplasia. A second transfusion of 80 cc was given into a scalp vein after which the values were red cells 4 190 000 hemoglobin 81 per cent

Subsequent counts were within normal limits One week after delivery the icterus index was 85 Since the child was not doing well despite normal counts another transfusion of 90 cc was given followed in three days by an additional 100 cc Vitamin K copperin B and liver extract were given empirically At 55 days she was discharged with deep mahogany colored skin slightly enlarged liver and spleen and weight of 6 lb 4 oz

Twin B weighed 5 lb 14 oz and was jaundiced but much less than Twin A Spleen and liver were not remarkable The first day blood showed red cells 4 550 000 hemoglobin 90 per cent white cells 21 600 polymorphonuclear neutrophils 72 per cent lymphocytes 24 per cent myelocytes 4 per cent poikilocytosis moderate 34 normoblasts per 100 white cells Transfusion of 100 cc Rh negative blood from a male donor was given into the anterior fontanel Blood on the third day showed red cells 4 000 000 hemoglobin 79 per cent Vitamin K copperin B and liver extract were given but no further transfusions Subsequent counts were normal At 15 days she was discharged weighing 5 lb 12 oz Both twins are thriving

It is not certain whether the father is genetically hetero or homozygous since the first four normal offspring might have occurred in absence of a placental defect lack of sensitization of the mother or low titer of antibody The last pregnancy resulted in single ovum twins so that they had identical genetic inheritance both were Rh positive and therefore subject to the same titer of antibody from the mother yet in one a severe hemorrhagic form of the disease developed whereas the other reacted only mildly and might have escaped notice were it not for the history and condition of her twin Demy conclude that the portion of the placenta serving twin A had a greater functional defect than that serving twin B resulting in more massive exposure to antibodies from the mother

Her serum caused strong agglutination of Rh positive red cells in the incubator when 0 1 ml serum or serum dilutions was mixed with 0 05 ml of 1–2 per cent blood suspension The difference between agglutination in warmth and cold was marked It was almost impossible to detect any agglutination on slides while the titer of the serum was 1 128 after incubation supporting Levine s statement that human anti Rh agglutinins usually are warm The titer of a sample of serum withdrawn 10 days later was only 1 64 and apparently weaker than at first examination It remained at this level after delivery about five weeks after first examination The action of this serum agreed completely with that of other anti Rh serums so there is no doubt that it contained true anti Rh agglutinins Nevertheless the baby belonging to group O though Rh positive did not show any symptoms of erythroblastosis foetalis and is healthy The fact that the mother was a primipara should be emphasized her future pregnancies and those of others like her should be observed

Erythroblastosis Foetalis in Identical Twins is reported by Nicholas George Demy[1] (New York Polyclinic Hosp)

Woman 40 seven times pregnant had had four successive living infants in 1924 1927 1929 and 1932 In 1934 she gave birth to twins one stillborn and the other dying of hemorrhage in four hours In 1936 a stillborn child 16 lb also had hemorrhage probably a case of fetal hydrops Erythroblastosis foetalis was suspected in the last gestation The father s blood was Rh positive the mother s Rh negative in high titer Labor resulted in normal spontaneous delivery of identical twin girls as shown by the single placenta single chorion and two amnions Microscopic examination revealed no abnormality

Twin A weighed 5 lb 8 oz was jaundiced and petechial hemorrhages appeared within 24 hours Spleen and liver were greatly enlarged and hard Blood the first day showed red cells 1 560 000 hemoglobin 40 per cent white cells 164 000 polymorphonuclear neutrophils 49 per cent lymphocytes 47 per cent myelocytes 2 per cent metamyelocytes 2 per cent

(1) Am J Ob t & Gyn c 47 554 556 Apr 1 1944

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Comparison of New Born Infants with Erythroblastosis Foetalis with Those Born to Diabetic Mothers Herbert C Miller Roswell D Johnson and Stanley H Durlacher (Yale Univ) point out that the syndrome in infants with erythroblastosis foetalis is similar in many features to that seen in some infants whose mothers either have diabetes mellitus or develop it later in life Twenty infants born of diabetic mothers were compared with 36 infants with erythroblastosis foetalis Changes common to both groups were increased normoblastemia extensive extramedullary erythropoiesis hypertrophy of the heart hyperplasia of the islands of Langerhans adrenal enlargement edema macrosomia and a tendency to hemorrhage in all tissues of the body There were two striking differences infants with erythroblastosis foetalis frequently have anemia and jaundice and the mothers red cells are Rh negative those born to diabetic mothers rarely have anemia or jaundice and distribution of the Rh factor in the maternal blood is similar to that in the general population

Hydrops foetalis congenital anemia of the new born and icterus gravis have been considered parts of a single syndrome because of familial incidence Levine and his co-workers have held that the syndrome and its familial pattern depend on iso agglutinins developed in the mother during pregnancy However it is difficult to reconcile this with the facts that about 10 per cent of mothers are Rh positive that in some Rh negative mothers no iso-agglutinins can be demonstrated despite the erythroblastosis foetalis in their infants and that there is no correlation between severity of the syndrome in the infant and the antibody content of the maternal serum [For other explanations of these facts see the preceding articles —Eds] This study shows why the iso immunization theory may not be true for all cases of erythroblastosis foetalis Unless all infants without anemia and jaundice are excluded some born to diabetic mothers will be included under the diag

( ) J Ped t 24 603 615 J 1944

nosis erythroblastosis foetalis Infants born to diabetic mothers rarely have anemia or jaundice but do have large numbers of normoblasts in the peripheral blood and extra medullary tissues and are similar to infants with erythroblastosis foetalis in many other important respects It is not clear whether Levine and others limited their diagnosis of erythroblastosis foetalis to infants with anemia and jaundice inclusion of infants born to diabetic mothers would account for the fact that some mothers were Rh positive Mothers need not have symptoms or signs of diabetes at the time of the infant s birth but may develop them later in life It would be most difficult to exclude infants who were stillborn or died in a few hours whose mothers had not yet developed diabetes and who were Rh positive since the premature death would preclude diagnosis of anemia and jaundice

Numerically the offspring of diabetic mothers are sufficient to account for the 10 per cent of infants whose mothers are Rh positive Further investigations will decide whether infants born to diabetic mothers or mothers with future diabetes should be included in the syndrome of erythroblastosis foetalis Arguments in favor of it are the strikingly similar somatic and visceral changes and the fact that some of the alterations in the various organs and tissues are found almost exclusively in these two groups of new borns

[The following articles dealing with cold hemagglutinins suggest a relationship between them and hemolytic anemia on the basis of the increased mechanical fragility of such agglutinated erythrocytes —Eds]

Cold Hemagglutinins in Acute Hemolytic Reactions in Association with Sulfonamide Medication and Infection *William Dameshek (Boston) reports three cases* in which acute hemolytic anemia developed during an acute infectious disease and following administration of sulfathiazole and sulfadiazine and in which a potent cold hemagglutinin was found Two patients had virus pneumonia The third

(9 J A M A 123 77 80 Sept 11 1943

patient had infectious mononucleosis in this case heterophil sheep cell agglutinins were also found One case is presented here

Man 26 had taken a total of 9 Gm sulfathiazole and 4 Gm sulfadiazine for an acute condition manifested by fever sore throat and cough He continued to have mild fever and one week after sulfonamides were discontinued he complained of passing dark urine He was pale and sallow and the red cell count was 3 700 000 On admission pallor was increased he was dyspneic and the urine was dark burgundy red with a heavy trace of albumin A transfusion was contemplated but could not be carried out for blood from numerous group O donors cross matched with the patient s serum (also in group O) by the slide method at room temperature was found to be incompatible The patient became worse pallor and dyspnea increased and jaundice developed A hemolytic streptococcus infection was diagnosed sulfadiazine was re administered and he became rapidly worse X ray examination of the chest suggested virus pneumonia His condition became critical The red cell count was under 2 000 000 and the leukocyte count 43 000 The red cells showed distinctive spherocytosis and polychromatophilia The hypotonic fragility test was 0 56–0 24 per cent The blood bilirubin was 3 6 mg per cent

Diagnosis of acute hemolytic anemia with hemoglobinuria was made and sulfadiazine discontinued Examination of the serum revealed a potent hemagglutinin which had the following characteristics greatest activity at 4 and 20 C agglutination titer 1 128 (serum dilution) inactivation at blood temperature (37 C) and 56 C reactivation when temperature was lowered to 20 C agglutinating activity against red cells of all group O individuals tested auto agglutination slight agglutination of guinea pig and rabbit red blood cells hemolysis in low titer of rabbit red cells in presence of guinea pig complement no isohemolysins or autohemolysins demonstrable The patient was given a transfusion of 500 cc compatible blood precaution being taken to keep the blood continuously warm throughout its removal from the donor and administration to the patient In addition by means of a U tube connection 350 cc of a 5 per cent sodium bicarbonate solution was given continuously during the transfusion His condition improved almost immediately and the next day the urine had lost its brownish red color He was given another transfusion and recovery was uneventful thereafter

It is possible that the combination of a high titer of ab

normal autohemagglutinins and of a sulfonamide might result in agglutination and injury of red cells in the patient own circulation and thus in development of hemoglobinuria and acute hemolytic anemia The authors have demonstrated that agglutinins injure the cell membrane making it susceptible to injury by trauma or stasis Use of the Landsteiner Levine test tube technic at both ice box (or room) and incubator temperatures instead of the prevailing slide technic at room temperature in testing for transfusion purposes is essential This not only will demonstrate the cold nature of the agglutinin but may demonstrate a warm hemagglutinin or hemolysin which has previously not been recognized Chilling of the patient with virus pneumonia and other conditions in which a cold hemagglutinin is found should be avoided Since severe transfusion reactions may occur in acute hemolytic anemia as few transfusions as possible should be given The blood should be kept warm constantly It is best not to use blood from a bank since the red cells already modified are more liable to injury Alkalization with sodium bicarbonate intravenously may reduce the severity of the renal reaction

Cold Agglutinated Erythrocytes Hemolytic Effect of Shaking Daniel Stats (Mount Sinai Hosp New York City) studied two cases of extremely high titers of cold hemagglutinins In each case hemoglobinemia was demonstrable by immersion of an extremity in cold water

The first patient had acute hemolytic anemia without hemoglobinuria during atypical bronchopneumonia Four days before apparent onset of anemia 6 Gm sulfadiazine had been given At the height of disease the cold hemagglutinin titer was 1 20 000 at 4 C At this time the in vitro hemolytic phenomena were present Thirteen days later when the titer had fallen to 1 800 at 4 C hemolysis was not demonstrable The second patient had symmetrical gangrene of tips of fingers and toes and hemoglobinuria after exposure to moderate environmental cold The cold hemagglutinin titer of 1/30 000 at 4 C was constant

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lysis requires shaking of the cells but not complement Hemolysis of cold agglutinated erythrocytes is different from hemolysis of the Donath Landsteiner test In the latter hemagglutination is slight erythrocytes sensitized in the cold by amboceptor are hemolyzed at 37 C by complement lysis failing to occur in the cold

Chronic Hemolytic Anemia with Auto Agglutination and Hyperglobulinemia Report of Fatal Case Roy R Kracke and Byron J Hoffman (Emory Univ) found no similar case reported in the literature

Woman 32 had had long standing severe intravascular red cell destruction accompanied by reticulocytosis numerous erythroblastic crises splenomegaly auto agglutination and hyperglobulinemia Cardinal features in this case were a high amount of globulin in the blood from an unknown cause and a strong agglutination of her own cells and of cells of members of all blood groups After many years of marked compensatory erythropoietic activity as indicated by reticulocytosis her bone marrow became unable to compensate and finally death occurred

Positive Wassermann Kahn Kline and Eagle reactions were elicited on several occasions her sister also had positive reactions to syphilis The positive serologic tests a microscopic granulomatous area in the liver section obtained at autopsy generalized atrophy of the hepatic cords and some irregular areas of fibrous tissue with round cell infiltration were strongly indicative of a chronic infection possibly syphilis An atypical type of familial hemolytic icterus was unlikely for the fragility test was negative and splenectomy did not effect a cure Mediterranean anemia in an adult with repeated erythroblastic crises is rare This possibility was suggested by the Grecian origin of her father but there was no evidence of bone rarefaction in roentgen studies or at autopsy The most likely diagnosis was therefore atypical chronic hemolytic anemia with auto agglutination hemolysis and hyperglobulinemia secondary to a chronic infection

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( ) A I t M d 19 673 684 O t be 1 43

over many months and the results of in vitro hemolytic tests were always found to be positive

EXPERIMENTS —These were done within three hours of collection of blood except on the old and old lyophylized serums used Blood or serum was stored at 37 C before use Inactivated serum was heated at 56 C for 1½ hour before use The old serum had been collected aseptically 15 months before use and stored at 6 C The old lyophylized serum was collected 15 months and lyophylized 14 months before experimenting It was made up to its original volume with distilled water before use The blood of the patients with cold hemagglutinins was used In all tests homologous or heterologous group O erythrocytes previously washed with 0 85 per cent sodium chloride solution were used Dilutions of the patients serums were made with 0 85 per cent sodium chloride solution or with normal serum of the same blood group Serologic tubes 10 × 75 mm were used The tests were set up and reactants mixed gently at 37 C Shaking of the tubes was done in standard manner at room temperature and completed in 10 seconds each tube was replaced in the rack at the temperature of that particular experiment In some of the tests final readings of hemolysis were made after sedimentation or centrifugation at the temperature of the experiment in others results were read after centrifugation at 400 rpm for two minutes at 22 C Since the final erythrocyte concentration was as high as 40 per cent in some experiments hemolysis was never complete

The results demonstrated the existence of a unique type of hemolysis dependent on a high concentration of erythrocytes *extreme potency of cold hemagglutination* and presumably damage as the result of shaking Concentrated erythrocyte suspensions subjected to marked cold agglutination were readily hemolyzed by shaking or tapping The amount of shaking was not sufficient to hemolyze relatively weakly agglutinated or nonagglutinated erythrocytes No hemolysis was observed when the cold hemagglutinin titers were lower than 1/2 500 at 4 C Similarly light erythrocyte suspensions even though strongly agglutinated in the cold were not hemolyzed Occurrence of hemolysis in absence of complement is especially interesting This phenomenon therefore is not entirely immunologic for

Cold Hemagglutination with Symmetrical Gangrene of Tips of the Extremities A case is reported by Daniel Stats and Jesse G M Bullowa (New York Univ)

Negro 64 stated that for 15 years he had noted tinglin burning and numbness of the tips of his fingers and toes on exposure to cold often accompanied by a sharp pain in the



Fig 48—Dry gangrene of finger tips two months after onset of gangrene

epigastrium The symptoms subsided after he entered a warm room The first urine passed after such episodes was dark coffee like Tingling or pain on exposure to cold was not experienced in the tip of the nose or ear lobes Two weeks prior to admission he was exposed to a temperature of 5 F for one hour He had the same symptoms as upon previous occasions however while the urine shortly resumed its normal

(3) Arch Int Med 7 506 51 October 1941

urine obtained before and after the experiment were tested for hemoglobin Hemolysis occurred only in the cold extremity and there was no hemoglobinuria indicating that it was a local phenomenon (*Fig 49*)

Further examination revealed negative tests for syphilis and no significant abnormality in the peripheral blood The rate of destruction of erythrocytes was found to be normal There were no signs of organic vascular disease The authors concluded that *the symmetrical gangrene of finger and toetips* was caused by cold hemagglutination

[The following articles deal with sickle cell disease which as a cause of both hemolytic anemia and various other conditions may be obscure unless diagnosed by special blood tests —Eds]

Sickle Cell Disease With Special Regard to Its Non anemic Variety In a previous communication [1941 YEAR BOOK OF GENERAL MEDICINE p 358] Bauer pointed out that the disease known as sickle cell anemia should be called sickle cell disease because anemia though the best known and most frequent sign of the disease is neither the essential nor the most dangerous one It is assumed that circulatory stasis in the small blood vessels of the internal organs is the primary and most perilous consequence of the sickling trait (sicklemia) Patients with this disease usually do not die of anemia but may die of circulatory stasis in some vital organ Since the sickling phenomenon is markedly enhanced by lack of oxygen and any condition that might diminish oxygen supply may become dangerous such patients are poor medical and surgical risks All Negro patients in medical and surgical services should be tested routinely for sicklemia to avoid many erroneous diagnoses such as rheumatic fever rheumatic heart disease polyarthritis osteomyelitis cerebral disease peptic ulcer appendicitis and cholecystitis

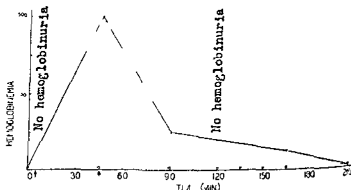
Julius Bauer and Louis J Fisher (Los Angeles County Gen l Hosp) report *six cases in which the pathologist* diagnosed sickle cell anemia in five of which this condition had not even been suspected by the clinician One case is cited here

Negress 26 complained of pain in the back chills fever

(1) A h S g 47 55 563 D ml 1943

less than one minute In two minutes the cells were tightly agglutinated giving the appearance of gel On changing the temperature to 37 C by immersion in a water bath breaking up of the massive agglutination was apparent in 30 seconds and in 2 minutes complete dispersion of the cells occurred

4 The venules and capillaries of the bulbar and palpebral conjunctivas were examined and found to be normal On



F g 49—Rel ti h p b tw n h mogl b em a and time after expo ure of fo e m to cold, hemoglob m xpr s d in mg hemoglobi p r 100 cc. Unb k n line blood ght a m b k n l ne blood left arm rows r ght f m and elb w at 4 C

irrigation of the conjunctival sacs with 100 cc iced isotonic solution of saline for 1½ minute marked segmentation of blood columns—apparently by clumps of erythrocytes—was seen with the slit lamp corneal microscope On exposure *of the eye to room temperature the segmentation slowly* disappeared The experiment illustrated the action of the antibody in vivo

The following experiment was carried out because the patient *gave a history of repeated passage of coffee colored* urine although hemoglobin was not found in routine urinalyses The right forearm was immersed in ice water and the left kept at room temperature After 10 minutes venous blood was withdrawn from the left arm and after 25 minutes from the right and left arms Thereafter both arms remained at room temperature At appropriate intervals for 1½ hour blood was drawn from both arms simultaneously The various specimens of plasma obtained by centrifuging the blood and

urine obtained before and after the experiment were tested for hemoglobin Hemolysis occurred only in the cold extremity and there was no hemoglobinuria indicating that it was a local phenomenon (Fig 49)

Further examination revealed negative tests for syphilis and no significant abnormality in the peripheral blood The rate of destruction of erythrocytes was found to be normal There were no signs of organic vascular disease The authors concluded that the symmetrical gangrene of finger and toetip was caused by cold hemagglutination

[The following articles deal with sickle cell disease which *as a cause of both hemolytic anemia and various other conditions may be obscure unless diagnosed by special blood tests*—Eds]

Sickle Cell Disease With Special Regard to Its Non anemic Variety In a previous communication [1941 YEAR BOOK OF GENERAL MEDICINE p 358] Bauer pointed out that the disease known as sickle cell anemia should be called sickle cell disease because anemia though the best known and most frequent sign of the disease is neither the essential nor the most dangerous one It is assumed that circulatory stasis in the small blood vessels of the internal organs is the primary and most perilous consequence of the sickling trait (sicklemia) Patients with this disease usually do not die of anemia but may die of circulatory stasis in some vital organ Since the sickling phenomenon is markedly enhanced by lack of oxygen and any condition that might diminish oxygen supply may become dangerous such patients are poor medical and surgical risks All Negro patients in medical and surgical services should be tested routinely for sicklemia to avoid many erroneous diagnoses such as rheumatic fever rheumatic heart disease polyarthritis osteomyelitis cerebral disease peptic ulcer appendicitis and cholecystitis

Julius Bauer and Louis J Fisher (Los Angeles County Gen l Hosp) report six cases in which the pathologist diagnosed sickle cell anemia in five of which this condition had not even been suspected by the clinician One case is cited here

Negress 26 complained of pain in the back chill fever

(3) A h S g 4 55 5 D b 1943

and vomiting for four hours Temperature on admission wa 98 2 1 pulse 96 and respiration 44 General rigidity of the abdomen was most marked in the left lower quadrant the whole abdomen was extremely tender There were stiffness of the neck and generalized muscular tenderness especially in *the extremities* *White blood cell count* was 9 500 polymorphonuclears 86 per cent and lymphocytes 14 per cent non protein nitrogen was 16 mg per 100 cc Phenolsulfonphthalein appeared in the urine in 4 minutes—45 per cent in 30 minutes 15 per cent in 1 hour No red blood cell count was done The patient died after three days of severe pain Autopsy revealed hemorrhagic splenomegaly and punctate hemorrhages *of the kidney Microscopic examination of sections* of liver and kidneys revealed sickling of red blood cells The cause of death was not determined

Although circulatory stasis in the small vessels of the splanchnic area and various muscles was not looked for the authors believe that this was the cause of the acute abdominal symptoms stiffness of the neck muscular tenderness and eventual death

The authors also present a history of a white patient

Girl 19 of Sicilian parentage was operated on for torsion of the spleen Splenomegaly with fibrinous perisplenitis wa found but no torsion Splenectomy was performed After operation marked sickling of the red blood cells was found and microscopic examination of the spleen revealed the typical picture of sickle cell disease There was practically no anemia but the icteric index was 44

The authors conclude that the following may occur in a person with the constitutional sickle cell trait (*1*) no further consequences may develop (2) sickle cell disease may develop as proved by anatomic findings chiefly in the spleen without noticeable impairment of health (*3*) actual sickle cell disease may develop causing circulatory stasis and producing manifestations of impaired circulation in various organs (4) more or less severe anemia may develop as the leading sign of sickle cell disease (5) sickle cell disease may be present and the patient may have severe *anemia different from sickle cell anemia* (6) he may become a victim of his constitutional biologic inferior

ity and succumb under circumstances innocuous to others

Rate of Sedimentation of Erythrocytes in Sickle Cell Anemia was investigated by Travis Winsor and G E Burch (Tulane Univ) In 6 of 10 patients the sedimentation rates were slow when compared with their packed cell volumes Those with the most severe anemia had the lowest sedimentation rates Additional anemia produced artificially in blood of patients who already had mild or severe anemia did not produce a comparable slowing of the rate It is therefore not the anemia itself which produces the slow rate but some other factor [probably degree of anoxemia of sample —Eds] which changes concomitantly with the decrease in erythrocytes There is strong indication that it is carbon dioxide per se [i e anoxia — Eds] and not the change in pH produced by carbon dioxide that slows the sedimentation rate The rate was rapid when rouleau formation was normal somewhat slow when it was abnormal and very slow when it was not present The slow rates seen when rouleaux were abnormal suggest that other factors besides rouleau formation affect the sedimentation of erythrocytes [i e cohesion of erythrocytes due to sickling —Eds]

The sedimentation rate of blood saturated with oxygen was invariably accelerated and that of blood saturated with carbon dioxide invariably retarded These results proved to be reversible by alternate saturation with the two gases Placing the blood from patients with sickle cell anemia in a vacuum of 780 mm Hg for 23 minutes accelerated the rate indicating that carbon dioxide retards sedimentation by mechanisms other than mere exclusion of oxygen [i e CO causes fall of pH and cell swelling —Eds] Inhalation of pure oxygen accelerated the rate as did exposure of blood to air Keeping a tourniquet on the arm for 10 minutes retarded the rate the same occurred on rebreathing into a paper bag

(4) A h I t M d 73 41 5 J 1 44

The findings support the value of oxygen therapy in the acute crisis of sickle cell anemia When operation is necessary an anesthetic gas that does not produce anoxemia is preferable Because various factors may influence the sedimentation rate in sickle cell anemia the method of studying the blood should be more standardized

[These experiments represent an indirect method of detecting increases in the viscosity of the blood occurring when the erythrocytes become sickled as a result of diminished oxygen tension Increases of as much as 120 per cent in viscosity have been induced by sickling in low oxygen tension and measured with the Ostwald viscosimeter by Ham and Castle (1940 YEAR BOOK OF GENERAL MEDICINE p 165) In the present experiments there is an additional retarding factor caused by increase in erythrocyte volume due to fall in pH resulting from the pure CO This becomes evident when contrasted with the experiments employing removal of oxygen by vacuum pump—Eds]

Congenital Hemolytic Icterus Elwood O Horne[5] (Worcester Mass) reports two cases associated with cholecystitis and cholelithiasis—frequently encountered complications Splenomegaly and jaundice were also present Both patients were in the younger age group yet presence of gallstones was a prominent factor In the first case splenectomy and cholecystectomy were performed in two stages with successful recovery in the second case splenectomy and cholecystostomy were accomplished in two stages 13 years apart followed by rupture of the cholecystostomy sinus into the peritoneal cavity with resultant biliary peritonitis and death Had cholecystectomy been performed subsequent to the first operation the end result would probably have been more favorable When hemolytic icterus and cholelithiasis are present a rational procedure would seem to be cholecystectomy and splenectomy in one or two operations splenectomy alone is not sufficient Splenectomy with cholecystectomy rather than cholecystostomy is the operation of choice and removal of the gallbladder is indicated more often than is believed

Hemoglobin Metabolism and Hematology in Congenital Hemolytic Jaundice during Clinical Crisis, Repeated

(5) Am J Surg 65 56 64 July 1944

Transfusions and before and after Splenectomy Reports in the literature cite liver enlargement repeated attacks of nau ea vomiting fever and progressive jaundice with upper right quadrant pain in presence or ab ence of gall stones and a direct van den Bergh reaction in the serum

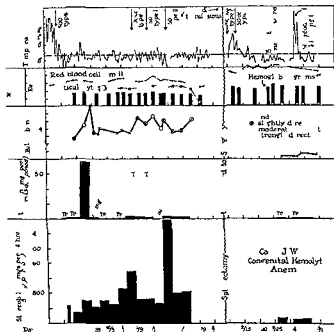


Fig 50—L b t ry d ta ca f g t l h m lyt j und

or one changing from indirect to direct during the acute period as clinical characteristics Pathologic reports include marked enlargement of the liver (no histologic studies) perilobular congestion of characteristic type and some degree of parenchymal degeneration varying from mild with recovery to severe with terminal acute yellow

atrophy Farrar's case showed moderate liver degeneration with recovery following splenectomy the clinical condition was aggravated by transfusions He and his associates suggest that an acute liver failure is one of the pathogenic mechanisms of the clinical crises observed in hemolytic anemia

Robert C Lowe (Louisiana State Univ) reports a case in which decreased liver function was observed during the crisis which cleared spontaneously There was no evidence of marked blood destruction Such changes have been noted in certain crises of sickle cell anemia Transfusions were followed by progressive enlargement of the spleen marked increase in blood destruction and drop of red blood cells hemoglobin and reticulocytes Probably the transfused cells were sequestered in the spleen and rapidly destroyed leading to the marked stercobilin excretion Splenectomy was followed by return to normal of the red blood cells hemoglobin reticulocytes bilirubinemia and pigment excretion All clinical symptoms and signs disappeared The tenderness and enlargement of the liver disappeared rapidly and has not returned The laboratory data are shown in Figure 50

Blood Changes Occurring during the Course of Sulfonamide Therapy are reviewed by N G Markoff[7] In acute infectious diseases the therapy effects a rapid crisis like normalization of the blood picture Of special significance is the rapid disappearance of toxic changes in the nuclei and protoplasm of cells in the peripheral blood and bone marrow

The toxic effects of sulfonamides on the blood and blood forming organs may be divided into two group The first includes cyanosis formation of methemoglobin sulfhemoglobin or methemalbumin and porphyria These changes are reversible and are not considered an indication for discontinuing the drug Treatment is necessary only in rare cases and consists of blood transfusion and injection

(6) Am. J M Sc 06 347 35 S pt mbe 1943
( ) Schw z. med. W h sch 73 656-66 M y 8 15 3

of 10 cc of 1 per cent methylene blue solution or of 20 mg niacin three times a day The second group of much greater significance includes (1) changes related to erythropoiesis (2) those related to leukopoiesis and (3) thrombocytopenic purpura

1 The appearance of inclusion bodies or Heinz s blue granules in erythrocytes has recently been studied extensively by Moeschlin and Hurschler They are small round single or multiple corpuscles appearing at the periphery of the red cells and stainable with the common reticulocyte stains They may be the first precursors of an impending anemia Hegglin and Moeschlin distinguish three degrees of inclusion body formation up to 200 per cent over 200 per cent and over 500 per cent The first degree has no clinical significance and interruption of chemotherapy is not necessary With the second degree there is no danger of hemolytic anemia and daily control of the blood smear is imperative chemotherapy should be continued only in case of vital indication The third degree indicates severe hemolysis and requires immediate withdrawal of the drug and administration of blood transfusions The types of anemia that may develop as a result of sulfonamide therapy include secondary anemia acute hemolytic anemia with inclusion body formation or *inclusion body anemia progressive hemolytic anemia* and aplastic anemia

The blood picture in hemolytic anemia induced by sulfonamide therapy shows anisocytosis macrocytosis a tendency to microcytic spherocytosis and a normal or slightly increased leukocyte count The diminished resistance of erythrocytes to hypotonic salt solution is [usually —Eds] not marked The serum bilirubin values are normal or slightly increased platelet count is normal The spleen is moderately enlarged as a result of increased activity and destruction of erythrocytes containing inclusion bodies at that site The bone marrow notably in inclusion body anemia shows pronounced erythroblastosis basophilia karyorrhexis Jolly s bodies polychromasia and

...rrar's case showed moderate liver degener... ...ers following splenectomy the clinical ... aggravated by transfusion He and his ... ...ct that an acute liver failure is one of the ... mechanisms of the clinical crises observed ... anemia

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(6) Am J M Sc 206 34 352 September 1943
(7) Schw ... [illegible] 1943

penia accompanying certain infectious diseases such as Bang s disease grip pneumonia measles pneumonia and certain Bacillus coli infections indicates a peripheral de struction of leukocytes and is no contraindication to sul fonamide therapy A rise in leukocytes usually results from chemotherapy In polycythemia vera there is danger of panmyelopathy (Greenwald) In acute and subacute leu kemia *sulfonamides are contraindicated because of the* danger of shocklike breakdown of marrow function with resulting panmyelophthisis There is less danger in chronic myelogenous leukemia [Chemotherapy which may correct secondary infection in acute or subacute leukemia is hardly more dangerous than the underlying conditions —Eds]

There is no sulfonamide which safeguards against dam age to the blood It is worthy of note that a peripheral toxic effect of a drug on erythrocytes is not necessarily combined with damage to the leukopoietic component of the marrow The toxicity of sulfonamides as regards blood damage *decreases in this order sulfanilamide sulfa* pyridine and sulfathiazole Aside from agranulocytosis and aplastic anemia the blood changes induced by sulfonamides are generally favorable

Symptomatic Hemolytic Anemia. I J Davis (Univ of Edinburgh) reports four cases of acquired hemolytic anemia associated with carcinomatosis reticulosis or Hodgkin s disease (two cases) subleukemic leukemia No patient had a personal or familial history of jaundice or any other evidence suggestive of familial acholuric jaundice

CASE 1 —Man 72 complained of pain in the back increas ing fatigue and weakness He was pale had moderate jaundice and enlarged liver with a hard uneven edge Laboratory ex aminations showed severe hyperchromic macrocytic anemia with persistently high reticulocyte count Sternal puncture re vealed hypercellular normoblastic marrow Icterus index varied between 23 and 50 and the van den Bergh reaction was positive indirect Urine showed excess urobilinogen without bilirubin or hemoglobin There was no evidence of hemorrhage He deteriorated despite hematinic therapy and transfusions and died of hypostatic pneumonia three weeks

(8) Edinburgh M J 51 083 Feb 1944

basophilic stippling The number of inclusion bodies is smaller than in the peripheral blood The hematologic signs are usually preceded by alarming clinical signs unexplained fever fatigue vomiting marked cyanosis a high degree of urobilinogenuria jaundice and bilirubinemia. The following factors aid in diagnosis of inclusion body anemia appearance on the third to seventh day of chemotherapy presence of minimal concentration of the drug in the blood peak of symptoms within two to four weeks and lack of increase in the anemia despite a constant concentration of the drug Treatment consists of early recognition of the danger signals immediate discontinuation of the sulfonamide forcing of fluids transfusions intrasternal injection of bone marrow obtained from a normal subject and administration of large amounts of liver extract niacin and vitamin B complex [Of these transfusion is the only measure likely to be useful —Eds]

2 Leukopenia appearing on the seventh to twentieth day of chemotherapy indicates suppression of marrow function and calls for withdrawal of the drug except in the presence of a vital indication The same applies to granulocytopenia Children are especially apt to develop the latter symptom Fever of obscure origin is the first danger sign lesions of the tonsils follow later Since there may be a latent period up to 27 days agranulocytosis may appear long after the drug has been discontinued In cases with possible pre existing damage to the bone marrow as in polyarthritis syphilis focal infections and liver damage even small doses of a sulfonamide may precipitate a sudden decrease in leukocytes

3 Thrombocytopenic purpura is probably due to hypersensitivity to the sulfonamide plus damage to thrombocytes and megakaryocytic function

Secondary anemia resulting from a streptococcic infection is usually improved with sulfonamide therapy The same applies to pernicious anemia or hemolytic icterus co existing with acute infections Pre existing aplastic anemia is a contraindication to sulfonamide medication Leuko-

axillae elbows and neck were enlarged soft di crete not fixed to the skin and not tender Tonsils liver and spleen were moderately enlarged and x ray examination showed en largement of mediastinal nodes Blood showed red cell 4,250 000 hemoglobin 80 per cent reticulocytes less than 1 per cent white cells 22 200 with polymorphonuclears 67 per cent lymphocytes 10 per cent monocytes 17 per cent eosinophils 3 per cent Turk cells 3 per cent Sternal puncture re vealed cellular normoblastic marrow with hyperplasia of the granulocyte series Histologic examination of a lymph node from the groin showed considerable hyperplasia of large hi t ocytes with vesicular nuclei Diagnosis was reticulo endo tl eliosis His condition remained stationary for three weeks with slight irregular fever Symptomatic treatment including ulfapyridine had no effect Jaundice then developed with icterus index 14 hemoglobin 37 per cent 1 720 000 red cells per cu mm and color index 1 07 The blood film showed 60 per cent reticulocytes with numerous nucleated red cells *White cell count rose to 31 900 without primitive white cells* Three days after this hemolytic crisis 2 pt blood was trans fused but a week later the red cell count had again dropped reticulocytes fell to 13 per cent and white cell count to 13 800 *X ray therapy and transfusions gradually produced improve ment* For three years his condition remained satisfactory then he was readmitted with dyspnea bilateral hydrothorax ascites and enlargement of liver spleen and lymph nodes in neck axillae *mediastinum* and groins *However the blood* howed no abnormalitie Sternal puncture revealed a normal picture except for increase in eosinophil granulocyte He died 10 days later

Autopsy disclosed wide pread enlargement of lymph nodes most noticeable in the para aortic groups All nodes were dis cr te firm and pale yellow Histologically the picture was that of vell advanced Hodgkin s disease Spleen howed areas of proliferating reticulo endothelial tissue with areas of necro i little hemosiderin and no erythrophagocytosis Liver showed only degenerative changes Marrow in femur and sternum showed reactive hyperplasia was very cellular and n rmoblastic Gray areas consisted of proliferating fibroblasts and endothelial cells accordingly considered a result of Hodg kin infiltration

Case 4 — Woman 41 a year previously was treated for mod rate anemia which despite icterus index of 17 and per sistent low grade reticulocytosis gradually improved When symptom of anemia became pronounced again she was

after admission Autopsy disclosed adenocarcinoma of the tail of the pancreas with meta tases in the liver left kidney and abdominal media tinal and deep cervical lymph nodes Marrow showed hyperplasia of the erythropoietic tissue but there was no involvement of bones (right femur ribs and sternum were examined) Histologic examination showed sidero is in pleen liver and marrow No iron pigment was seen in any tumor cells The histiocytes of the spleen and Kupffer cells of the liver displayed hyperplasia and evidence of phagocytic activity

CASE 2—Youth 19 complained of progres ive weakne s and pallor Three years before a swelling in the right side of the neck diagnosed as lymphadenoma had subsided under x ray treatment and did not recur He was thin pale slightly jaundiced Tongue was clean and moist Two slightly enlarged glands were found in the right inguinal region The lower edge of the pleen was a handbreadth below the costal margin Blood examination revealed normochromic slightly macrocytic anemia with persistently elevated reticulocyte count Icterus index was 25 Urine showed excess urobilinogen but no hemoglobin or bilirubin Sternal puncture showed cellular marrow with normoblastic erythropoiesis but a section of the clot obtained at puncture revealed in addition to fragments of marrow tissue small areas of abnormal tissue composed of undifferentiated polyhedral cells of varying size There were some large cells with large polymorphic reticular nuclei and a few multinucleated cells The picture was that of reticulo endothelial proliferation and warranted diagnosis of reticulosis He was given iron fresh yeast and liver extract but he deteriorated jaundice deepened and blood count fell progressively to 995 000 per cu mm although the reticulocyte count continued elevated and leukopenia persisted Transfusion was given He died some weeks later Autopsy was not obtained

The grounds for assuming that an abnormal hemolytic mechanism was operating in this case are not as evident a in Case 1 The progressive anemia and elevated reticulocyte count might have come from widespread disturbance of the marrow but there was no immaturity of the peripheral white cell picture as is seen in leuko erythroplastic anemia nor were there nucleated red cells

CASE 3—Man 50 complained of weakness slight fever and generalized rash of three weeks duration The rash was composed of red discrete maculopapules Lymph nodes in groins

ovarian teratomas (West Watson and Young Singer and Dameshek) in which removal of the tumors resulted in hematologic recovery

No convincing evidence has been submitted that any significant degree of erythrophagocytosis or other form of red cell destruction occurs in tumor tissues In hemolytic anemia secondary to reticuloses widespread erythrophagocytosis has been described The patients suffered from severe anemia which appeared to be hemolytic in origin Cases 2 and 3 may be examples of such histiocytic medullary reticulosis Another possibility is that products emanating from the underlying pathologic lesion may exert an injurious effect on the circulating red cells rendering them unduly prone to destruction Davis suggests that the neoplastic process may exert an abnormal stimulus to increased activity of the reticulo endothelial cells The phagocytic activity in spleen and liver noted in Cases 1 and 4 is compatible with this theory It is difficult however to reconcile this theory with the development of microspherocytosis and increased red cell fragility reported in some cases

Physiologic Intravascular Hemolysis of Exercise Hemoglobinemia and Hemoglobinuria Following Cross Country Runs D Rourke Gilligan M D Altschule and E M Katersky (Harvard Univ) studied the intravascular hemolysis as measured by the appearance of hemoglobinemia and hemoglobinuria in groups of athletes following 2 6–26 2 mile cross country runs The plasma bilirubin red cell fragility hematocrit reading and urinary albumin and sediment were also studied

Hemoglobinemia was observed in 5 of 11 young athletes who ran 2 6–2 8 miles in 5 of 11 athletes who ran 4 5–5 1 miles and in 18 of 22 men who ran 26 2 miles Hemoglobinuria was observed in one of the athletes on three occasions after 5 mile runs It occurred in 4 of the *22 men who ran 26 2 miles* the urines were brownish to

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markedly pale and had moderate icterus and a large firm adherent swelling on the right jaw of a month s duration. Spleen was moderately enlarged Menstrual periods had been irregular and lately she had constant blood loss per vaginam. Icterus index was 20-25 the van den Bergh reaction was strongly positive indirect Urine contained excess of urobilinogen without bilirubin or hemoglobin Feces contained large amounts of urobilinogen The Hess test for capillary fragility was positive Blood showed red cells 1,480 000 hemoglobin 24 per cent color index 0 81 mean cell volume 1?1 cu microns white cells 5 000 platelets 20 000 reticulocytes 66 per cent Films showed anisocytosis poikilocytosis and marked polychromasia Increased diameters of the reticulocytes gave a pseudomacrocytic appearance to the film Normoblasts were abundant The high mean cell volume was doubtless due to the numerous reticulocytes and normoblasts Promyelocytes were relatively frequent and a few myeloblasts were present Sternal puncture showed normoblastic erythropoiesis most cells were promyelocytes and myeloblasts warranting diagnosis of subleukemic myeloid leukemia

During hospitalization excessive red cell destruction and increased blood regeneration were constant After 14 days fever melena hematuria and purpura developed and the swelling of the jaw became purulent Transfusions and sulfathiazole were ineffective and she died in a month The white cell picture remained essentially the same throughout Autopsy confirmed the diagnosis of acute myeloid leukemia accompanied by normoblastic blood crisis Marrow in the middle of the femoral shaft was hyperplastic with normoblasts and primitive white cells of the granular series Spleen contained a moderate infarction pulp was infiltrated by myelocytes myeloblasts and many histiocytes some containing iron pigments Lymph node enlargement was confined to the para aortic groups with myelocytic infiltration and hemosiderosis Liver showed fatty degeneration and abundant free iron with myelocytes and myeloblasts in the sinusoids Kupffer s cells were hypertrophied and displayed phagocytosis of hemosiderin Numerous petechial hemorrhages were present in pericardium esophagus stomach and renal calices

The mechanism of hemolysis in these cases is obscure and may well vary according to the nature of the primary pathologic process That the hemolytic mechanism is not necessarily dependent on invasion of the marrow is shown in two reported cases of hemolytic anemia associated with

two cases One of these two new cases is presented here

Man 21 complained during route marches of abdominal discomfort followed by passing of red urine Symptoms promptly cleared with rest. General examination was negative An attack was induced by a march of 8 miles On cystoscopy red dish brown urine was noted in the bladder and dark smoky urine was spurting from ureteral orifices There were only a few red cells but benzidine reaction was strongly positive The patient was observed for three months during which time 40 paroxysms were induced Blood counts were normal at the beginning and end of the study No abnormalities were noted in the blood cells ordinary plasma constituents or urine before and after a paroxysm apart from the hemoglobinemia hemoglobinuria and slight albuminuria after erect exertion This indicates that only small amounts of blood were involved in the episodes Attempts to reproduce the attacks by fever multiple minor traumas and exercise in recumbency or on a *bicycle and to influence attacks by ascorbic acid alkalization* of the urine and wearing a tight abdominal binder were negative

The authors believe that the hemoglobinemia characteristic of the paroxysm may not be due to increased hemolysis but to an abnormality which permits the accumulation of hemoglobin in plasma This conclusion is based on the following facts (1) All observers failed to demonstrate hemolytic agents or blood abnormalities predisposing to increased hemolysis (2) the amount of hemoglobin involved in all the paroxysms in the authors cases and in most reported cases could be liberated in the normal destruction of senile erythrocytes (3) 15 minutes after exertion the plasma hemoglobin values show a significant drop toward the resting level whereas with a hemolytic factor involved a longer lag would be expected (4) previously reported observations on fecal urobilinogen suggest that during paroxysms there may be no increase in blood destruction

[A logical but not very phy ological set of reasons —Eds]

Studies in Destruction of Red Blood Cells III Mechanism and Complications of Hemoglobinuria in Patients with Thermal Burns Spherocytosis and Increased Osmotic Fragility of Red Blood Cells Shu Chu Shen

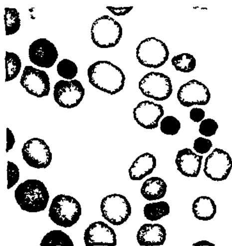
dark burgundy red Observations on one of these four athletes showed hemoglobinuria again after a 20 mile run Occurrence of intravascular hemolysis was unrelated to age body build or standing position of the runners or to the number of years or state of their training Hemoglobinemia and hemoglobinuria disappeared a few hours after the end of the run It has been calculated that the amount of blood destroyed intravascularly is very small Spectrophotometric studies of the plasma and urine revealed conclusively that the plasma and urinary pigment were hemoglobin and not myoglobin There were no methemalbumin bands in the plasma and the Schumm test was negative in three runners with plasma hemoglobin values of 20–44 mg per cent The plasma bilirubin was distinctly elevated after the marathon run This may have been due to decreased liver function consequent to hepatic ischemia during exercise The fact that hyperbilirubinemia occurred in the presence or absence of hemoglobinemia demonstrates that it did not result from intravascular hemolysis the degree and duration of hemoglobinemia were not sufficient to give rise to such high levels of bilirubinemia The erythrocyte fragility was normal after marathon runs Transient albuminuria was observed frequently after the 2 6–5 1 mile runs and in every instance after the marathon run Transient urinary excretion of formed elements occurred frequently after the shorter runs and in almost every instance after marathon runs

Hemoglobinemia sometimes accompanied by hemoglobinuria occurs in man frequently enough after strenuous runs to be considered physiologic under these conditions and comparable in its apparently benign nature to the albuminuria of exercise The findings of this study are of particular importance at this time when young men in the armed forces are accomplishing strenuous physical feats

March Hemoglobinuria R A Palmer and H S Mitchell[1] (R C A M C) review the literature and report

(1) Ca J M A J 49 465 472 December 1943

erved value of 520 mg hemoglobin per 100 cc urine Maximal excretion of hemoglobin occurred during the first 12–24 hours then decreased rapidly Proteinuria other than hemoglobinuria occurred in the first 24–48 hours to a marked degree in five cases and to a moderate degree in six Oliguria occurred in the first 24–48 hours in most of the severely burned patients with or without hemoglobinuria Chronic azotemia of moderate severity occurred despite re establishment of adequate excretion of



F g 5 St d blood m d 60 hou aft b rn h w g d n ely ta d ph ocyt nd so f g d form R d ed f m 1 000

urine in four of five patients with hemoglobinuria who lived five days or longer In six patients with hemoglobinuria examined post mortem the histology of the kidneys was consistent with hemoglobinuria The immediate treatment of severely burned patients should include administration of fluids and alkali to assure diuresis of neutral or alkaline urine

No significant anemia occurred during the first 24–48 hours in the 14 patients in whom detailed study was pos

Thomas Hale Ham and Eleanor M Fleming[2] (Harvard Univ) report observations on 40 patients with combined second and third degree thermal burns involving 15-65 per cent of the body area Eleven showed hemoglobinuria The series included 34 patients burned in the Cocoanut Grove disaster and 6 others

In eight cases hemoglobinemia was observed during the first 20–36 hours with values ranging from 65 to 215 mg hemoglobin per 100 cc plasma Spectroscopically

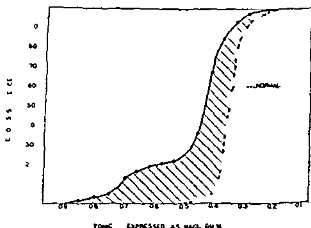


Fig 51 —Curve of osmotic fragility of red cells obtained two hours after burn involving 30 per cent of body and three hours before death.

oxyhemoglobin and methemalbumin were detected in the serum examined from one patient The urine samples from patients with gross hemoglobinuria were scanty in amount for one or two days varied from black to red to light brown were acid (pH 4 5–5 8) and contained hemoglobin in solution in precipitated form and in casts The red and brown pigments were identified spectroscopically as oxyhemoglobin mixed with traces of methemoglobin There was no evidence of myohemoglobin The amount of hemoglobin varied from traces in two cases to a maximum ob-

(2) New England J Med. 229 701 713 Nov 4 1943

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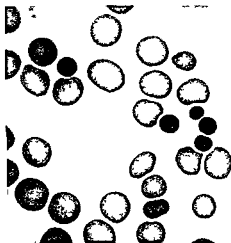


Fig 5 —St d blood m m d 60 h ft b h w g d n ely ta d ph ocyt d som f g t d f m R d d f m 1 000

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No significant anemia occurred during the first 24–48 hours in the 14 patients in whom detailed study was pos

sible 10 of whom had hemoglobinuria Osmotic fragility of the red cells was significantly increased above normal in seven patients five of whom had hemoglobinuria An extreme increase in osmotic fragility occurred in one patient burned 30 per cent (Fig 51) Blood smears from certain of the burned patients showed fragmentation budding spherocytes and microspherocytes of the red cells Maximal fragmentation of red cells was seen only in the smears taken promptly after the burn Deeply staining spherocytes were detectable in one case 60 hours after the burn (Fig 52) No cold or warm agglutinins or hemolysins were detected in the blood samples with osmotic fragility

Heating of human blood in vitro to 51-65 C produced irreversible and progressive fragmentation and formation of spherocytes a progressive increase in osmotic fragility and hemolysis of some of the red cells in plasma serum or isotonic solution These cells also showed increase in susceptibility to hemolysis by trauma It is assumed that the increased osmotic fragility of heated red cells results from conversion of the normal biconcave to a more nearly spherical form by a process of progressive fragmentation Blood of dogs was heated sufficiently to cause increase in osmotic fragility and then injected into the animal Blood samples removed immediately after injection showed abnormal osmotic fragility and stained smears showed spherocytes *Presumably red cells susceptible to hemolysis in vitro in isotonic sodium chloride were subject to* osmotic hemolysis in vivo in the isotonic plasma

The authors findings and experiments suggest that in persons with thermal burns destruction of a considerable volume of erythrocytes may result directly from heating at the site of the burn depending on the temperature attained by the blood duration of heating and volume of blood subjected to these conditions Accordingly the thermal changes in the blood may not correlate strictly with the area burned but may be anticipated in extensive third degree burns

'Heat Resistance' of Erythrocytes Robert Hegglin and Conrad Maier* (Univ of Zurich) describe a specific test for recognition of Marchiafava's anemia a relatively rare disease Symptomatology consists chiefly of nocturnal hemoglobinuria constant hemosiderinuria pseudomacrocytic anemia with tendency to regeneration of bone marrow increased reticulocyte count in peripheral blood and leukopenia The osmotic resistance test of the erythrocytes is normal According to Ham and others the disease is due to the action of a hemolysin whose amboceptor is always present in the erythrocytes In presence of complement hemolysis takes place The degree of hemolysis increases as blood pH falls The test demonstrates the decreased resistance of erythrocytes in this condition to increased temperature

The test consists of putting a test tube containing about 5 cc blood obtained by a dry air sterilized syringe into the incubator for 6–24 hours at 37 C Presence of hemolysis of clotted blood in vitro evident to the naked eye after six hours at this temperature appears to be pathognomonic specific evidence of Marchiafava's anemia In pernicious anemia slight hemolysis may sometimes be observed if the blood remains in the incubator for 48 hours at 37 C but this is never more than 150 mg per ml Quantitative determination of the degree of hemolysis i e hemoglobin content of the serum is practically unnecessary but if desired it may be done according to the method of Wu Hsien Hemolysis increases greatly if the blood is shaken from time to time in the incubator Degree of hemolysis does not permit conclusion regarding the phase or stage of the disease

[This test does not depend on the heat resistance of the erythrocytes but on the accelerated acid production caused by the increased temperature of the incubator This can readily be shown by the inhibition of the effect of incubation by addition of alkali to the blood —Eds]

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PERNICIOUS ANEMIA AND RELATED MACROCYTIC ANEMIAS

The first five articles in this section testify to the effect [of] interest in pernicious anemia maintained in the Chicago area especially at Cook County Hospital —Eds

Erythrocyte Damage by Lipemic Serum in Normal Man and in Pernicious Anemia Victor Johnson L Willard Freeman and Joan Longini (Univ of Chicago) t[h]e that several mechanisms protect against exposure of eryth rocytes to too high concentrations of injurious fatty acids and soaps including absorption of products of digested fat into lymphatics dilution of hemolysin in the thoracic duct slow emptying of chyle into the blood and mixing of hemolytic chyle with large volumes of blood in the subclavian vein and heart Erythrocytes of normal man are rendered more susceptible to hypotonic hemolysis in a standard fragility test by exposure to lipemic serum This constitutes further evidence that fat ingestion is one factor in the normal daily destruction of red blood cells

A high fat diet in normal animals does not cause enough increase in daily erythrocyte destruction to produce anemia Normal marrow can replace these extra losses of red blood cells In untreated pernicious anemia lipemic serum produced not only an increased erythrocyte fragility but actual hemolysis when lipemic serum and red cells of the same

osmotic he... were mixed In contrast lipemic serum of ade
The authors ... pernicious anemia patients and of normal
persons with their ...ly increased fragility but no actual
treated ... erythro... own red blood cells On exposure to
produced on the ... normal man erythrocytes of patients
...sis of their ... nemia were rendered more susceptible
...c serum of ... olysis as revealed by standard fragility
pernicious a... red cells in normal individuals certain
...ypotonic hem... than pernicious anemia and treated perni
than were ... Excessive destruction of erythrocytes by

the digestion products of fat is probably one of the etiologic factors in pernicious anemia because of a more than normal sensitivity of pernicious anemia red blood cells to such products A deficient plasma protection against these materials may also be involved

Summary of 80 Living Cases of Pernicious Anemia is presented by Maurice Hardgrove (Gorgas Hosp Ancon C Z) Robert Yunck Hugo Zotter and Francis Murphy (Milwaukee County Hosp) Data were obtained by interviews with the patients and supplemented by study of case records

Ages varied from 37 to 83 most patients being 60–69 Fifteen per cent of cases were first discovered between ages 40 and 49 earliest age of suspected onset was 29 Commonest presenting symptoms were progressive weakness and fatigue Dyspnea dizziness ankle edema palpitation paresthesias sore mouth and gastro intestinal complaints were frequent More unusual were hemorrhagic tendencies precordial pain difficulty in walking nervousness insomnia bitter taste in the mouth and fainting Tinnitus was present in six cases when anemia was severe and disappeared after red cell count became normal In most cases there was weight loss Diagnosis was not made until two years after onset of suspicious symptoms in 20 per cent Fifty one per cent of patients had been treated over 5 years and 17 per cent over 10 years the maximum being 13 years

Study of predominant national groups showed 67 per cent of patients German Polish or Irish Countries of northern Europe and the British Isles were the origin of forefathers of over 87 per cent However it must be remembered that Milwaukee is primarily a German and Polish settlement There were one Italian and one Negress For 43 accurate diagnosis was not made by the first physician consulted although suggestive symptoms were present For 11 per cent the first three physicians con

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sulted did not make a correct diagnosis 86 per cent were not adequately studied until hospitalized 95 per cent were hospitalized for diagnosis or early treatment

Seventeen patients had transfusions soon after hospitalization Results did not agree with Jahsman s statement that with use of parenteral liver extract transfusion is rarely needed Strauss states that transfusion is indicated if air hunger or signs of circulatory failure are present at rest in the severely anemic patient About 14 per cent were gray before 30 and almost 28 per cent before 40 One patient 41 with pernicious anemia diagnosed at 39 reported that her hair was white during the acute stage of illness and with treatment turned to dark brown Photographs and hair samples confirmed this About two thirds of the patients had gray blue or green eyes agreeing with Isaacs and Friedlander s findings of predominance of light eyes in these patients

Sore tongue was initial symptom in 56 per cent 38 per cent never had a tongue complaint Four had occasional glossitis after beginning treatment but it had not been an initial complaint Sore tongue recurred at intervals of as long as seven and nine years Paresthesias at onset occurred in 71 per cent and in 27 of these disappeared under treatment while the remainder continued to notice them occasionally or constantly In most intensity decreased under treatment Numbness tingling and burning were cardinal symptoms principally in hands and feet A few complaints were referred to the chest arms and entire lower extremities Difficulty in walking was a complaint of 41 per cent at onset but only 17 per cent complained of this both at onset and after treatment Almost all reported improvement Some difficulty in walking not present at onset developed in 10 per cent even with apparently adequate therapy In 55 per cent numbness tingling and burning in the hands and poor co ordination and grip were present with almost all showing considerable improvement under treatment Some bladder difficulty oc

curred at onset in 32 per cent. In 21 per cent, bladder complaints at onset persisted after treatment, while in 57 per cent frequency developed during therapy. Frequency was most common, and there were several cases of incontinence and a few of minor difficulty in urination. One patient had acute retention, another cystitis and two moderate prostatic hypertrophy. Gastro-intestinal complaints occurred in 82 per cent and degenerative heart disease in 17 per cent.

Treatment was designed to keep the red cell count between 4,500,000 and 5,000,000 and hemoglobin values above 80 per cent. Maintenance of weight also seemed to be an important guide as to efficiency of treatment. This was accomplished in [illegible] per cent of cases by one injection of 1 cc crude liver extract 1 unit every four weeks, and in 11 per cent every three weeks. In individual cases more frequent injections were required. Reactions to injections of liver extract, usually allergic, occurred in 27 per cent of cases and in five it forced change to oral therapy. Nineteen patients discontinued treatment for three months to five years, but all subsequently resumed it. Time elapsing before severe relapse occurred varied greatly in different cases.

Pernicious Anemia in Negroes is said to be rare. The findings of Steven O. Schwartz and Maurice Gore contradict this statement. Of a total of 1,600 cases of pernicious anemia seen at Cook County Hospital between 1931 and 1942, [illegible] occurred in Negroes, giving a ratio of whites to Negroes of 10:1. Since the ratio of all admissions to the hospital during this period was 2:1, the corrected ratio is about 5:1 or 20 per cent. These figures correspond to an incidence of about 170 cases per 100,000 white patients and [illegible] cases per 100,000 Negro patients. Of the Negro patients [illegible] were males and [illegible] were females; the ratio in the white population was 1:1. More than two thirds of the [illegible] patients were between the ages of 40 and 70. How-

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per week for the remainder of hospitalization Patients disappeared from observation at intervals ranging from immediately after discharge until 45 months later Nearly always discontinuance of therapy was voluntary Average amount of liver given during the period was 10–400 units [U S P] per month depending partly on individual need and partly on regularity of attendance

The patients relapsed at intervals of 2–38 months About 33 per cent relapsed during the first six months 36 per cent during the next six months 24 per cent during the second year 5 per cent during the third year and about 1 per cent later No arbitrary erythrocyte level was used for criterion of relapse In each case the relapse represented an incapacitating illness with levels so low at times as to be barely compatible with life The highest blood level during relapse was 2 600 000 and the lowest 430 000 Multiple relapses were frequent one patient had 12 relapses during 10½ years the last one complicated by fractured femur resulting in death (Fig 53)

No correlation was demonstrated for age sex race duration of treatment previous to abandonment of therapy total amount of liver given or average dose and the relapse period It is suggested that the amount of intrinsic factor secreted the diet storage capacity of the liver and some other unknown factors influence the duration of remissions Previous studies attempting to evaluate massive dose therapy and storage of liver extract appear to be inaccurate because they do not take sufficient cognizance of the highly individualized behavior of patients with pernicious anemia during remissions

Cardiovascular Manifestations in Pernicious Anemia Considering the chronicity of pernicious anemia some mechanism of compensating for the deficit of hemoglobin and resultant decrease in tissue oxygenation must exist The increased cardiac output represents this compensatory mechanism The fewer erythrocytes by moving with increased velocity make their oxygen carrying capacity more

ever there were many more below 40 and far fewer over 70 than among Caucasians It is assumed that the first difference is due to the earlier precipitation of pernicious anemia owing to poor diet the second could be attributed to a shorter life expectancy The type of the disease observed is identical in Negroes and whites

Relapses in Pernicious Anemia. Steven O Schwartz and Helen Legere (Cook County Hosp) report on 54 patients readmitted because of recurring symptoms of pernicious anemia in relapse some time after successful liver therapy of previous relapse All relapses resulted from discontinuance of therapy either immediately after discharge or months or even years after satisfactory maintenance had been established All patients were from a low economic

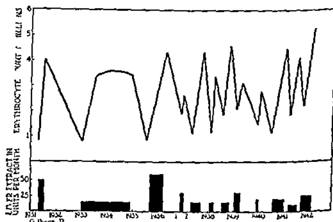


Fig 53—Tw l e el p 10 y du t self n glect.

level and depended on financial aid Diets were probably suboptimal in animal proteins vitamin B factors and vitamin C Usual treatment was administration of 1 unit [U S P] of liver daily for 15 days (most patients were used for the purpose of assaying liver) then 60–90 units

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ett (Cen l Hosp) report pathologic findings in the central nervous system in two cases of pernicious anemia with subacute degeneration of the spinal cord and brain

Cerebral and spinal cord lesions were almost identical In both the essential pathology consisted of more or less diffuse though uneven degeneration of the white matter



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with little or no proliferation of fibrous glia The changes were unique and quite unlike those that occur in cerebrovascular disorders multiple sclerosis and other chronic degenerative disease In the cerebrum the affected white matter was diffusely but unevenly pale when examined in sections stained for myelin the unevenness being due to a more pronounced degeneration in some regions usually around blood vessels (Fig 54) In many such foci varying in size from 50 to 1 0 microns myelin was completely

frequently available This mechanism leads to changes in the heart J Bailey Carter and Eugene F Traut (Univ of Illinois) on reviewing records of 300 authenticated cases of pernicious anemia found 257 with and 43 without cardiovascular manifestations

No attempt was made to segregate those having primary cardiac disease in the classification according to cardiovascular manifestations An outspoken relationship was noted between cardiovascular complaints and anemia With improvement in the condition of the blood the cardiovascular symptoms lessened Anemia may bring out cardiac signs in a patient with involvement of the heart In four of six patients with mitral stenosis symptoms first developed with onset of anemia Two of these were relieved with improvement in the blood picture Occurrence of cardiovascular symptoms and findings with hematologic decompensation and their disappearance following treatment or during remission was striking in the present series Angina or any cardiovascular symptom may be the initial or outstanding evidence of severe disease of the blood These manifestations even when accompanied by distinct graphic changes such as low voltage displacement of the S T interval or even definite flattening of the T wave do not necessarily mean primary heart disease Symptoms and findings are not restricted to any type of anemia or related to its severity Hematologic examination is the only dependable means of differentiation It is important in angina to rule out anemia as a determining or contributing factor especially if the angina is associated with palpitation dyspnea enlarged heart systolic murmur low arterial pressure edema or urobilinogenuria If anemia is present a therapeutic test may be necessary to determine its role in the production of cardiac symptoms

Subacute Degeneration of Brain in Pernicious Anemia Raymond D Adams and Charles S Kubik (Massachu

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0 02-0 03 cc maximum 0 05 cc They do not consider a reaction positive unless the wheal is over 15 mm in diameter or unless pseudopods are present Similar tests with hog and beef muscle are usually negative

Although a few of the reported reactions to liver extract are probably due to preformed histamine most are on a true allergic basis The sensitivity is to some substance—possibly the antianemic factor—in liver extract irrespective of its biologic source Symptomatic treatment consists of administration of adrenalin or ephedrine and calcium preparations for the generalized type and use of calamine lotion with phenol for urticaria and pruritus Desensitization is recommended for patients who react frequently

The authors began desensitization with 0 1 cc of a 1 10 dilution and increased the dose by about 0 2 cc every second or third day for about three weeks until the patients were receiving the average full therapeutic dose They believe it important to keep this type of patient desensitized by giving the therapeutic injection in smaller quantities and at more frequent intervals than is customary i e at least once a week

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HYPOCHROMIC ANEMIAS

Serum Iron in Health and Disease Joan F Powell (Oxford Univ) reports on serum iron values in 70 normal controls and in patients with various types of anemia A menstrual periodicity in the serum iron of normal women was demonstrable Rather low values were obtained in hemolytic anemias this is explained on the assumption that iron was being removed from the serum for hemoglobin regeneration at about the same rate as hemoglobin breakdown was going on in the reticulo endothelial cells Since simultaneous storage of iron may also be taking place in these cells raised serum iron levels may be expected

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degenerated Axis cylinders as well as myelin sheaths were affected though possibly not to the same extent In the perivascular zones of more severe degeneration were numerous macrophages filled with fat The number of astrocytes and oligodendrocytes was increased throughout the white matter more so just beneath the cortical gray matter than in the deeper white matter where the myelin was more severely degenerated The astrocytes had large cell bodies and cytoplasmic processes distinctly stained in Nissl s preparations The order of involvement of the central nervous system seems to be posterior columns then lateral and anterior columns and finally cerebral white matter Analysis of these two cases and of others indicates that patients with brain lesions have mental symptoms although the converse is not necessarily true The authors tend to believe that both subacute combined degeneration of the spinal cord and subacute degeneration of the brain represent an advanced stage in a specific process that is induced by a deficiency of certain substances necessary to the metabolism of myelinated nerve fibres Not every patient with pernicious anemia will have demonstrable brain lesions but all those in whom there are definite and disseminated brain lesion will probably have mental disorders

Allergic Reactions to Liver Extract Robert E Kaufman Laurence Farmer and Carl Reich (New York City) review 50 cases from the literature and report 11 cases Brand of extract and dose have little relation to the occurrence of reactions Reactions usually occur after numerous well tolerated injections especially after a long injection free interval Of the 61 patients only 6 were definitely stated to be allergic The commonest symptom was urticaria Angioneurotic edema and asthma were reported in many cases and practically every allergic sign and symptom was mentioned No fatalities occurred

Reactions to intracutaneous tests with various brands of diluted liver extract are usually positive The authors ue

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poikilocytes In the most severe case there was an unusual number of macrocytes probably a response by the marrow to the marked lack of iron There was no direct sign of hemolysis since no case showed any reticulocyte increase or urobilinuria serum bilirubin and erythrocyte fragility to saline were normal Seven patients (including the man 45) who could be observed responded well to iron by mouth

Thomson emphasizes several points Overt blood loss apparently plays no part in causation of the anemias [Growth during adolescence with corresponding increase in blood volume is of course a form of overt blood loss —Eds] Careful inquiry failed to reveal any definite lack of dietetic iron In general the patients were fond of iron rich food—possibly a compensatory phenomenon The high incidence of hypochromic anemia in the first few years of life and its comparative rarity in school children suggest that in the present cases there is a specific deficiency the high incidence of defective gastric acidity suggests a connection between this deficiency and the anemia Since nine of the cases were found on routine examination of recruits the condition may be more common than realized

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OTHER ANEMIAS

The articles in this section deal with anemias other than pernicious hemolytic and hypochromic which are covered in preceding sections Of particular therapeutic interest are the group of refractory anemias with cellular marrow described by Davidson and his associate which apparently eventually responded to vigorous treatment with transfusions and liver extract —Eds

Deficiency and Dyshemopoietic Anemias of Infancy and Childhood Roy R Kracke and William R Platt (Emory Univ) classify anemias of infancy and childhood into two major groups (1) inadequate supply absorption or utilization of some essential nutrient or mineral resulting in deficient red blood cell formation—so called defi

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only during acute hemolytic crises when the rate of hemoglobin breakdown is greater than that of iron utilization and iron storage by the reticulo endothelial cell In some patients with hypochromic anemia and low levels the serum iron increased surprisingly after administration of iron therapy In two patients a satisfactory response was obtained only after simultaneous administration of vitamin C and examination of this phenomenon showed that effectiveness of small doses of iron may be greatly increased by simultaneous administration of ascorbic acid

Serum iron in a small group of men with vitamin C deficiency did not differ from normal values However the lowest value recorded was obtained in a patient with scurvy On treatment with ascorbic acid the value rose steadily

Hypochromic Anemia in Adolescent Males M L Thomson[3] reports observations on hypochromic anemia in nine adolescent recruits The case of a man 45 is also included to illustrate the later course of the untreated disease In each case anemia was first noted in early or middle childhood Except in one case there was no history of serious illness No patient had hemorrhage bleeding piles or jaundice family history in regard to anemia or jaundice was negative Some youths looked small and immature for their age most had not started to shave There were no symptoms except for slight breathlessness in the more severe cases The youths had pale smooth skin with no evidence of jaundice The tongue was smooth in four cases In nearly all cases there was a typical apical systolic murmur of hemic origin The spleen was just palpable in four cases it was enlarged two fingerbreadths below the costal margin in the most severe case Four patients had spoon nails All but one had deficient gastric acidity five had complete achlorhydria and four hypochlorhydria Hemoglobin values were 36–58 per cent (Haldane scale) the blood picture showed typical microcytes ring cells and considerable anisocytosis with some

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therapy supplemented by administration of iron and vitamin concentrates Several patients required blood transfusions to maintain life during the refractory period all eventually recovered

The essential data on six cases of idiopathic origin are presented in the table The average age of these patients

HEMATOLOGIC AND CLINICAL DATA

	C se 1	C 2	C 3	C E 4	C SE 5	CASE 6
Ag	46	[illegible]	5	5[illegible]	41	34
S	M	M	F	F	F	F
Red ell						
H l l	28	3	18	31	22%	18%
C t (M ll on)	1 17	0 89	0	1 31	0 86	0 75
C l d	1 19	1 30	1 16	1 19	1 28	1 0
R t locyt	<1	<1	<1	<1	<1%	<1%
M yt	+	+	+	+	+	+
Wl t l t	1 400	800	1 000	3,200	2 200	1 300
Pl t l t	Sc ty	S ty	S ty	S ty	S ty	S t
H m f t hl hyd	+	F HCl	+	+	F e HCl	+
D t f ymptoms b f b pit l t	6 mo	6 m	1	3 y	18 m	8 mo
D f f y p od	8 wk	4 wk	10 wk	4 wk	7 wk	5 wk
H m gl b d sch g	75	86 /	88	82	85 /	85
S bseq t t tm t	None	Non	N	L t t	N	L t t
D t f b- seq t bse a- t	20 mo	15 m	12 m	8 m	15 m	18 m
H m gl b n when l seen	105	90%	90	88%	98%	99

was 41 years In no case was enlargement of the liver spleen or lymph glands noted One patient showed manifestations of purpura In all six the anemia presented morphologic features similar to those of pernicious anemia of equivalent severity Sternal marrow films showed the characteristics of pernicious anemia in a stage of relapse However except in Case 2 initial sternal puncture was made after the patient received several injections of liver

ciency anemias (2) those from hemopoietic dysfunction Under deficiency anemias are the following

- I Iron deficiency anemias
  - a) Premature type
  - b) Infantile type
  - c) Childhood type
  - d) Adolescent type
  - e) Alimentary type
    - 1) Celiac disease
    - 2) Diarrheas and dysenteries
    - 3) Intestinal parasites
    - 4) Other gastro intestinal disorders
- II Vitamin C and D deficiency anemias
- III Thyroid deficiency
- IV Erythropoietic deficiency anemias
  - 1 Goat s milk anemia
  - 2 Pellagrinous anemia
  - 3 Dimorphic anemia of malnutrition
  - 4 Diphyllobothrium latum anemias
  - 5 Gastro intestinal disord rs
  - 6 Hepatic anemias

Under dyshemopoietic anemias are the following subtypes

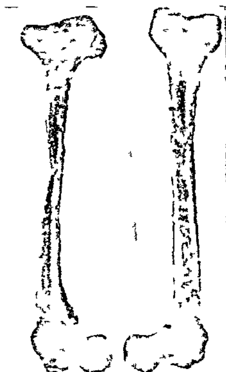
1. Congenital hypoplasia
2. Infectious aplasia
3. Chemical aplasia
4. Leuko erythroblastic anemia
5. Primary tumor anemia
6. Splenic anemia (Banti s syndrome)
7. Hepatic anemia
8. Nephritic anemia

Studies in Refractory Anemia Refractory Anemias with Cellular Marrow L S P Davidson L J Davis and James Innes (Univ of Edinburgh) divide the cases into two groups (1) refractory anemia with hypercellular megaloblastic marrow and (2) refractory anemia with cellular normoblastic marrow and arrested myelocyte maturation—chronic granulocytopenia

The authors discuss 16 cases of the first type In 10 reported previously occurring in pregnancy and puerperium severe anemia with hemoglobin readings of 17–52 per cent and megaloblastic sternal marrow was refractory for two weeks *to four months* despite intensive parenteral liver

(5) Edinburgh M J 50 431 441 July 1943

later had p ntancou hemorrhages fr m the ,um The hem atolrgic changes apparently preceded the bone change for o teo eler sis was n t discovered until hi It ho pital ad mi ion Peripheral blood change \ ere characterized l\ n evere normochromic normocytic anemia Color index varied between 1 0 0 9 an l 0 8 Volume in lex was 0 94 and m an corpu cular volume 90 On two early occ ion the leukocyte



l —S l t f mu l d m t f m w ca ty

count wa 44 810 and 80 000 sub equently it varied between 13 300 an l 5 600 reaching the lower levels in the late stages Peripheral bl od smear consi tently showe l leuko-erythro

extract i e at a time when patients with classic pernicious anemia should show normoblastic marrow The essential differential diagnostic criterion is thus a failure of response to parenteral liver therapy with preparations of known potency in the absence of sepsis or other factors known to interfere with therapeutic response in classic pernicious anemia All responded to intensive treatment after a refractory period of 4–10 weeks The recovery of these patients and those of the preceding group stresses the necessity for energetic measures to maintain life by repeated blood transfusions and continuance of intensive liver therapy in this type of anemia The excellent prognosis in this group is in contrast to the gloomy outlook for the group of refractory anemias with hypocellular normoblastic marrow

Two cases of the second type illustrate an anemia refractory to treatment of any kind They differ from classic agranulocytosis in the chronic course co existence of moderately severe anemia and absence of exposure to leukocytoxic agents It is debatable whether such cases should be classified as chronic refractory hypoplastic anemia or on account of the intense leukopenia as chronic idiopathic agranulocytosis Pentnucleotide had no appreciable effect on the total white cell count in either case but appeared to increase the percentage of polymorphonuclears slightly in one furthermore it resulted in an abscess with production of pus despite the fact that at the time peripheral white cell count was less than 1 000 with only 5 per cent polymorphonuclears

Leuko Erythroblastic Anemia with Diffuse Osteosclerosis Joseph Mendeloff and Julius Rosenthal (New York City) report a case

Man 57 complained chiefly of anemia the disease had run a progressive course for seven years and did not respond to splenectomy or to liver or iron therapy Numerous transfusions appeared only to prolong life but had no effect on the disease During the fifth year of illness he had a severe hemorrhage following extraction of a loose tooth and three months

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and liver became palpable while he was under observation Hemoglobin content had dropped to 62 per cent erythrocyte count was 3 070 000 leukocyte count 4 050 with myeloblasts 8 per cent non egmented neutrophils 11 per cent segmented 20 per cent lymphocytes 54 per cent monocytes 4 per cent eosinophils 2 per cent plasma cells 1 per cent normoblasts 2 per 100 white blood cells and platelet count was 40 000 Sternal aspiration showed an almo t completely myeloblastic marrow thus establishing diagno i of myeloblastic leukemia

From September until death in March 1942 he was under observation The white count remained low In October the blood studies showed hemoglobin 58 per cent erythrocytes 3 000 000 leukocytes 7 300 with myeloblasts 44 per cent pro myeloblasts 1 per cent myelocytes 3 per cent nonsegmented neutrophils 5 per cent segmented 4 per cent lymphocytes 36 per cent monocytes 3 per cent eosinophils 1 per cent 6 normo blasts and 1 erythroblast per 100 white blood cells He was sustained by repeated blood tran fusions yet hemoglobin values continued to drop especially during numerous febrile episodes Purulent otitis media and mastoiditis ended in gen eral terminal epsis On last admission hemoglobin content was 23 per cent and white count 800 with 20 per cent myelo blasts 1 per cent myelocytes 2 per cent nonsegmented neutrophils 14 per cent segmented 62 per cent lymphocytes and 1 per cent monocytes De pite sulfathiazole administration for the otitis media temperature ro e to 106 F and he died eight months after onset of first symptoms

Autopsy revealed a pale emaciated body with numerous petechiae over trunk and extremities and gums covered with clotted blood The heart was dilated flabby and pale The myocardium showed diffuse yellowi h mottling cau ed by local fatty changes in the muscle Microscopic collections of myeloid cells were found in the epicardium The lungs showed bronchopneumonia and abscesses Hilar lymph nodes were en larged soft and anthracotic Alveoli in the pneumonic areas were filled with fibrin and a varying admixture of red and young myeloid cells but few polymorphonuclears There were many small focal collections of myeloid cells around the bronchi

Liver showed numerous ab cesses filled with pus Lobular architecture was blurred There was distinct cellular infiltra tion of the periportal fields In addition to lymphocytes there were numerous young myeloid cells Kupffer s cells were prominent The abscesses were often surrounded by collec t ons of myeloid cells and mall cells with dark nuclei and

blasto i Shortly before death the platelet count was 110 000 No abnormal platelets were seen Pathologically the outstanding features were leuko erythroblastic anemia cardiac hypertrophy myocardial fibrosis extensive giant cell accumulation in the spleen bone marrow and lymph nodes and extensive osteosclerosis

Rhoads and Miller considered the problem of aplastic anemia associated with osteosclerosis in an analysis of idiopathic progressive anemia they distinguished five subgroups from histologic examination of bone marrow (1) aplastic anemia with aplastic marrow (2) aplastic anemia with hyperplastic marrow (3) aplastic anemia with active marrow (4) aplastic megakaryocytic marrow (5) aplastic anemia with sclerotic marrow More recently Rhoads substituted the name of primary refractory anemia for aplastic anemia By this classification the present case although not one of aplastic anemia could be considered one of refractory anemia with osteosclerosis

[Other synonyms for this patient s disease are nonleukemic myelosis (Hickling) or agnogenic myeloid metaplasia (Jackson and Parker) Other excellent illu trations appear in the original —Eds]

Osteosclerosis, Myelofibrosis and Leukemia Jacob Churg and Max Wachstein (Mount Sinai Hosp New York City) report that among 97 cases of leukemia 6 showed varying degrees of myelofibrosis without osteosclerosis Four of these were of the chronic myeloid type and x ray therapy was given in the other two diagnosis was subacute myeloid leukemia and x ray therapy was not given One of the latter cases is given here

CASE 1 —Youth 18 in July 1941 complained of severe low back pain and fever The only physical finding was moderate *generalized enlargement of the lymph nodes* *Blood studies* showed hemoglobin 80 per cent red cells 4 120 000 white cells 4 650 with neutrophils 56 per cent lymphocytes 42 per cent monocyte 2 per cent and no abnormal cells in the smear Enteric fever and infectious mononucleosis were considered *but temperature dropped promptly pain subsided* and he was discharged with diagnosis of grip Readmitted after five weeks he had pain in the left chest and fever and enlargement of the lymph nodes was more prominent Spleen

(7) Am J M Sc 07 141 15 F b a 1944

the connective tissue were small numbers of myeloid cells (Fig 57) occasional erythroblasts and rarely megakaryocytes In places the meshes were filled with pink stained homogenous material In others the process of marrow replacement appeared to have progressed further Vascular spaces were less prominent connective tissue denser and bone marrow cells almost totally absent In these areas there was also formation of new bone trabeculae Focal collections of myeloid cells were also found in kidneys and pancreas The cecum showed two small ulcerations surrounded by lymphocytes myeloids and few neutrophils

The changes in the bone marrow of the two cases in which x ray treatment was not given were of an essentially similar type The available sections of bone showed a varying degree of fibrosis In Case 2 the marrow was cellular and characteristically leukemic fibrosis was represented by a meshwork of fine threads of connective tissue there was no appreciable change in the bony trabeculation In Case 1 however the bony trabeculation was somewhat denser than normal with occasional areas of newly formed bone The hematic cells had all but completely disappeared from the marrow which was made up almost entirely of young mucoid rather cellular connective tissue

[Compare with the preceding article —Ed]

Histoplasmosis in Infant, with Autopsy Hans G Schlumberger and Allen C Service (Philadelphia) report a case

Boy 7 weeks old was admitted for treatment of a hydrocele of the right testis and died 2½ weeks later Delivery was normal after eight month gestation weight at birth was ... Family history was negative

Examination revealed the skin pale but not icteric superficial abdominal veins prominent and abdomen protuberant Rectal temperature was 101 4 F pulse and respirations were rapid Mucous membranes were pale Heart was apparently normal Liver and spleen were enlarged the tip of the spleen being felt almost at the pelvic rim There were a small umbilical hernia and a right sided hydrocele Diagnosis was bronchitis and secondary anemia with splenomegaly and hepatomegaly of unknown origin

Red cell count was 2 400 000 hemoglobin 7 5 Gm plate

[illegible] Am J M S [illegible]

cmty cyt plcm cither lmph cyt r atypical myeloblast Numer u granule t hem t l rin were tound inside and out ide th liver cell The pleen hd white infarcts near the upper p l Secti n h w l th malpighian corpuscles fairly num r u but v ry mall Architecture was well preserved lth ugh l th red and whit pulp wer infiltrated by very y ung m l id cell Infiltrati n w r cl rather than diffuse nd e p cially pr minent in the perifollicular zones There

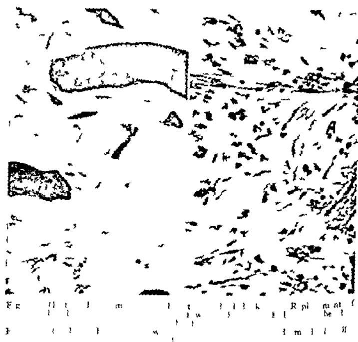


Fig ... R pl m nt f ... be l ... t m ll ...

v r atter l m g h t yt n l mall n t f er thre bla t Hem id rm s t und in larg quantitie l mph nod wer ett and pinkish r l All h w d a little m l l metapla i ith me blit r n f n rm l archite tur

Marrow of the v rtebral lumn w r l and most but in many place pale Ir and gr ecti n at differ nt level howed in general a v id ning f th trabecula without narrowing f intertrabecular p In m t ection the normal marrow was repl ced b l s ry l connective tissue (Fig 56) urr unding l ular p c In the mi ble of

POLYCYTHEMIA

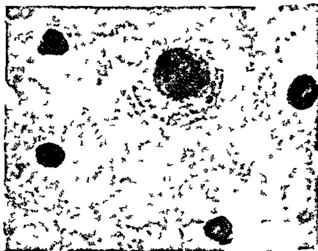
The two articles included in this section present two methods of controlling polycythemia vera both of which have been used by others. A third method, administration of phenylhydrazine, has also received extensive trial. In our opinion graded venesection is the most physiologic of these methods because it inhibits hemopoiesis by producing an iron deficiency. Phenylhydrazine therapy is the least physiologic as it increases the rates of both blood destruction and blood production and may lead to thrombosis. Many patients with polycythemia treated with venesection live so long that it seems to us wise if possible to avoid the potentialities for delayed marrow injury by x ray. —Eds

Control of Polycythemia Vera by Venesection. After a *detailed study of two patients for more than a year* Laurence E Hines and William C Darnall (Northwestern Univ.) find that venesection properly used is a safe method for controlling the disease. At first large venesections were performed which produced a sharp fall in erythrocyte volume, hemoglobin, specific gravity and viscosity and brought partial relief of symptoms but caused undesirable symptoms and erythropoietic stimulation. It was then found that no symptoms were produced by small venesections. There was gradual reduction of hematocrit values, blood viscosity and hemoglobin. The fall of hemoglobin was not equaled by a corresponding fall in numbers of circulating red cells because the latter had become microcytic. Four months after cessation of bleeding in one case and five months in the other the return of symptoms was associated with rise in hemoglobin and erythrocyte volume. Again a series of small bleedings was instituted.

The authors suggest the following method for control of symptoms of polycythemia vera. To determine the actual excess of circulating erythrocytes and to confirm the diagnosis an estimation of the total erythrocyte volume is made. At weekly or bimonthly intervals 200-250 cc blood is removed by *venesection done in the office with a 100 cc* syringe. The bleedings are continued until the computed excess of erythrocytes is removed or until hematocrit

(9) Am J M S 06 4 4 438 O t b 1943

lets 97 000 leukocytes 6 100 with 20 per cent neutrophil 77 per cent lymphocytes and 3 per cent monocytes Three normoblasts were found as well as moderate anisocytosis and poikilocytosis Urine contained a faint trace of albumin and 3–8 leukocytes per high power field All other tests were negative There was increasing difficulty in breathing and feeding After two transfusions of citrated whole blood hemoglobin content rose to 12 Gm red cell count to 3 660 000



F g 58 —Smea f m t l bta d by pl n m n tu In nt of fi ld m cyte t ng t y t f m f H topl m p l t m W gl t t ✓ bo t 1 00

leukocytes to 5 800 with 40 per cent neutrophils 60 per c nt lymphocytes platelets reached 175 000 There was never frank bleeding but there were minute petechiae on buttock and chest about 14 days after admission The sixteenth day a splenic puncture was done Histoplasmosis had not been suspected but smears revealed the typical yeast forms of the fungus in the monocytes (Fig 58) A tibial marrow study revealed the same bodies Another splenic puncture was done and the marrow and splenic pulp were streaked on blood agar plates from which organisms were subsequently isolated in pure culture He died two days after diagnosis of histoplasmosis Autopsy confirmed diagnosis as did subsequent culture and mouse inoculation

infectious mononucleosis which occurred during August 1942 in an E M S hospital and was apparently widespread in the surrounding districts Age incidence was 20–45 except in two women 84 and 64 Controls from nearby communities gave positive Paul Bunnell reactions and showed typical blood pictures whereas controls from more distant localities gave negative reactions indicating a definite localization of the disease The most interesting feature of the epidemic was the occurrence of cases without clinical manifestations

Incubation period varied from 5 to 10 days Severe intermittent frontal headache was present in 92 cases mental symptoms in 31 severe meningitic symptoms in 5 polyuria in 34 enlarged lymph nodes in nearly all the nodes in the posterior triangles of the neck and in the axilla being most frequently involved splenic enlargement in 50 skin rashes in 10 sore throat in 35 but severe angina in only 4 latent jaundice as indicated by the icteric index and the van den Bergh reaction in 8 of the severe cases In most cases the symptoms subsided in 5–21 days in a few the disease continued for longer periods with relapses

Of the 296 hospital patients tested 202 had positive Paul Bunnell reactions at 1 64 titer and over The titer 1 32 was suggestive and an indication for repeated testing Total white blood cell count varied from 8 000 to 20 000 but only a few had 20 000 Polymorphonuclears showed immaturity and stab cells were often seen many of the polymorphonuclears showed toxic granulation Early in the disease eosinophils were not present and basophils were 1–3 per cent Platelet count and coagulation time were unaffected The mononucleosis usually varied from 45 to 60 per cent in a few cases exceeding 75 per cent There was almost complete disappearance of small lymphocytes early in the disease whereas there was an increase in large and abnormal lymphocytes Examination of the sternal marrow in several cases revealed a definite increase in lymphocytic cells and a slight increase in activity in the myeloid series

hemoglobin and erythrocyte values reveal beginning are mm Bimonthly estimations of hemoglobin erythrocyte count and hematocrit will detect recurrence of the erythremic state and indicate the need for further venesection

Roentgen Irradiation in Polycythemia Vera by Multiple Small Doses to Large Areas of the Body Laurence I Robbins (Massachusetts Cen l Hosp) reports on 20 cases treated during the past 10 years with small doses The method cau ed no definite ill effects and resulted in longer rem ssions than with other forms of therapy

Technic —D ul le c at 20–50 r were given in these cases T tal d es varied from 200 to 1 200 r per series most patient r ceiving 500–600 r per eries The field covers the body from kne to neck This i accomplished by using a 20 × 20 cm cone on the machine and a target skin distance of 215 cm The field i centered at the level of the crest of the ilium and alternate anterior and posterior fields are used Other factor are 200 kv 0 5 mm Cu plus 1 mm Al filter giving a half value layer of 0 92 mm Cu Calculation of the output of the machine is determined with the Victoreen r meter measured in air at the actual target kin di tance and by the inverse quare law The pre ent daily dose is 20–30 r for a total of bout 500 r per one erie i e 250 r anteriorly and 250 r p teriorly Weekly white blood counts are done until a normal range i reached they are then checked daily A fall in white blood c lls below 4 000 or 000 warrants interruption of treatment During treatment the red blood cell count and hemoglobin do not usually change greatly but if after two or three months the cell count ha not fallen satisfactorily the ur f treatm nt ma be repeated cautiously

INFECTIOUS MONONUCLEOSIS

The leukocytic r p n t viru inf ctions are often small or other than polym rph n lear Ac rding to Bernstein, about 5 per cent of case of inf ct ous mononucleosis nev r exhibit a po itive Paul Bunnell reaction Included in this ection are two articles concerning patient with lymphocytosis and a negative Paul Bunnell reaction The e cases are contrasted with tho e of infectious mononucleo i in which the predominating cells are abnormal lymphocytes —Ed

Infectious Mononucleosis James P A Halcrow Lloyd M Owen and Norman O Rodger describe an epidemic of

(1) Am J Roentg 1 51 30 35 F b u y 1944
( ) B i M J 2 443 447 Oct 9 1943

Presenting Symptoms of Patients with Infectious Mononucleosis

Single Chief Complaint	/	Sore Throat	Fatigue	Headache	Cold	Fever	Enlarged Nodes	General Aches and Pains	Gastro-Intestinal Symptoms	Chills	Sore Eyes	Cough	Sweating	Dizziness	Earache	Combination of Two or More Symptoms	Grand Total
		Combination of Two Presenting Symptoms															
Sore throat				4	1	1	8	10				1				27	96
Fatigue	14															69	83
Headache	6	4			2	1	1	3								25	44
Cold	7			2		1		1								32	43
Fever	1	1			1	1		5	1	4						28	42
Enlarged nodes	4															35	39
General aches and pains	1	10		3	1	5					1					0	3
Gastrointestinal symptoms	2					1								1		13	17
Chills	0					4		2								5	11
Sore eyes	2			2				1								6	11
Cough	0	1														10	11
Sweating	0						—									6	6
Dizziness	1						—		1							2	4
Earache	0						—									4	4
Total	71	1	0	11	16	14	9	22	2	6	3	1	0	1	0	2	434

Treatment was mainly symptomatic In two anginous cases sulfapyridine was given but the condition became worse One patient with meningitic symptoms responded to sulfadiazine

Infectious Mononucleosis Andrew W Contratto (Harvard Univ) analyzed 196 cases The disease is benign accompanied notably by lymphadenopathy splenomegaly jaundice Vincent s angina ulcerations of the throat fever sometimes a morbilliform rash a conspicuous change in the blood picture and other complaints similar to those of an ordinary infection of the upper respiratory tract Accurate diagnosis is difficult because of variability of the symptoms and clinical manifestations Presenting symptoms are shown on page 379 Differential diagnosis is easily accomplished by the heterophil test blood count and smear frequent tests are necessary because there is often a delay of days or even weeks before the hematologic changes are conclusive enough to permit accurate diagnosis *Heterophilic agglutinations* however may not be positive for some days Therapy is nonspecific and includes bed rest and symptomatic treatment otherwise treatment is directed toward the accompanying symptoms such as codeine for headache and throat discomfort hydrogen peroxide for Vincent s angina salt for profuse sweating and intravenous injections of salt and dextrose for jaundice with nausea and vomiting During convalescence rest sleep, proper diet and fresh air are of great importance since extended fatigue is the most insidious characteristic of the disease

Acute Thrombocytopenic Purpura in Infectious Mononucleosis Putnam C Lloyd (M C A U S) states that occurrence of various hemorrhagic phenomena is now recognized as not being extremely unusual in infectious mononucleosis although in earlier descriptions of the disease it was stated categorically that purpuric and petechial eruptions did not appear Epistaxis has always been common

(3) Arch Int Med 73 449 459 Jan 1944
(4) Am J M Sc 9? 6 ? (? M 1944

In a man 30 characteristic lymphocyto is with numerous large lymphocytes and atypical mononuclear forms combined with a heterophil agglutination of 1 512 established diagnosis of infectious mononucleosis beyond a doubt despite absence of significant lymphadenopathy and palpable spleen Associated thrombocytopenia was difficult to explain since it could not have been due to depre sion or dysfunction of marrow in absence of anemia leukopenia and sternal marrow changes Presumably a combination of vascular damage resulting from acute infection and loss of circulating platelets at the purpuric sites was responsible for the widespread hemorrhagic phe nomena The platelet count of 66 may have been an expression of a transient toxic effect exerted peripherally rather than centrally

Severe infectious mononucleosis may in its early stages be indistinguishable from acute lymphatic leukemia and presence of purpura has long been considered an important diagnostic point in favor of the latter Lloyd s cases illus trate that purpuric and hemorrhagic phenomena with or without thrombocytopenia cannot constitute a valid distin guishing feature between these conditions Marked anemia i however rare in mononucleosis and if it appears with out obvious explanation the leukemic process may be suspected

Acute Infectious Lymphocytosis Peter A Duncan (St Luke s Hosp New York City) reports a case which dif fers from previously reported cases of acute infectious lym phocytosis by presence of clinical signs and symptoms at the on et

Girl 5 complained of abd minal pain first noted on the day of admi sion Because f boardlike rigidity and tender ness an acute abdominal condition was suspected but the blood count suggested a bl od dy crasia The spleen was not enlarged Small cervical and inguinal lymph nodes and a larger on in the left axilla were palpated Abdominal pain and rigid ty subsided after 10 hours in the hospital the pain returned for a short time on the fourth day During the first few days there were irritability headache lethargy nausea and projectile vomiting all suggestive of involvement of the nervous system Temperature was elevated with a peak of 103 F the fourth day For the rest of the even weeks of

(5) Am J D Ch ld 66 7 1 Septemb 1943

however Tidy and Daniel reported one or more episodes of nosebleed at various stages of the illness in 8 of 24 cases Similarly hematuria is fairly common as shown in 6 per cent of 270 cases collected by Tidy in 1921 While severe it is not usually associated with casts or functional disturbances and rarely if ever is precursor of acute nephritis Rectal bleeding is seldom prominent

Development of hemorrhagic skin eruptions is moderately frequent and merely one of many rashes described in this disease Petechial and purpuric hemorrhages may occur anywhere in the skin or mucous membranes larger ecchymoses are seen and in some cases a positive tourniquet test is noted in all these cases the blood platelets being normal in number and no other indications of a hemorrhagic diathesis being present Occurrence of true acute thrombocytopenic purpura with infectious mononucleosis is rare Williams in 1931 reported his own case in which a purpuric rash developed with a positive tourniquet test and prolonged bleeding time no platelet count was done Minot in 1936 reported three cases in which severe thrombocytopenic purpura was accompanied by lymphocytosis and varying lymph node enlargement In the only one in which the heterophil agglutination test was done it was negative Downey and McKinlay reported nine cases two with purpuric phenomena but no gross hemorrhages no platelet counts were done Cottrell's group of 12 cases included 1 in which a platelet count of 77 600 was found but no hemorrhagic manifestations and another without evidence of bleeding in which a platelet count was 45 000 Perhaps the most authentic case of true purpura and mononucleosis was that reported by Magner and Brooks in which hematuria bleeding gums purpuric eruption prolonged bleeding time and estimated reduction in platelets were combined with lymphocytosis palpable spleen moderate enlargement of inguinal nodes and a Paul Bunnell test of 1 800 the entire condition clearing up in six to eight weeks Lloyd reports one of these rare cases

present The heterophil agglutination reaction is uniformly negative Biopsies of lymph nodes from two cases showed a strikingly similar microscopic appearance consisting in degeneration of the lymph follicles and striking proliferation of the reticulo endothelium of the sinuses Serologic reactions were negative for lymphocytic choriomeningitis and influenza A and B virus The etiologic agent may be an undetermined virus related to infection of the upper respiratory tract In all case the disease was uncomplicated and had a favorable outcome

AGRANULOCYTOSIS

Agranulocytosis and Aplastic Anemia after Arsphenamines James W Fergu on (Glasgow Royal Infirm) reports six cases of bone marrow depression following neoarsphenamine treatment of syphilis Five had agranulocytosis and one showed depression of all marrow elements

The classification of blood dyscrasias following arsphenamine is not entirely satisfactory McCarthy and Wilson in 1932 suggested three main divisions (1) thrombocytopenic with a subgroup thrombocytopenic and granulocytopenic (2) granulocytopenic and agranulocytotic and (3) aplastic In the thrombocytopenic type the reaction occurs immediately or shortly after an injection and is characterized by purpura hemorrhages low platelet count and quick recovery Apart from the low platelet count blood picture is normal Rapid reappearance of platelets is not in keeping with toxic depression of megakaryocytes Falconer and Epstein were able to return a great number of platelets to the circulation in such cases by injection of 1 cc epinephrine hydrochloride and suggested that the condition is an allergic phenomenon In view of the different mechanisms of production and the highly favorable prognosis in these cases of simple thrombocytopenia it

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hospitalization she was practically afebrile and asymptomatic.

Hematologic data were similar to those described in previous cases There was relative and absolute lymphocytosis of approximately five weeks duration Neither atypical nor immature lymphocytes were observed throughout the course. The predominant type of cell found on biopsy of the bone marrow was the small mature lymphocyte Additional hematologic changes were observed early in the course An initial myeloid stimulation was indicated by an increase of the total neutrophil count on the first day However this dropped rapidly to extremely low levels on the fifth and seventh days this may indicate some suppression of myeloid tissue at those times. The persistently low platelet count during the first nine days supports this assumption The Paul Bunnell test was negative.

Acute Infectious Lymphocytosis Specific Infection. Carl H Smith (Cornell Univ) saw four cases of acute infectious lymphocytosis within three weeks Three were in one family and one in a hospital contact Analysis of these and five other cases shows that acute infectious lymphocytosis represents a specific entity distinct from infectious mononucleosis acute lymphatic leukemia and miscellaneous infections associated with lymphocytosis The disease is both infectious and contagious and has a possible incubation period of 12–21 days Hyperleukocytosis with relative and absolute lymphocytosis due to increase in normal small lymphocytes constitutes the most important diagnostic feature Elevated blood levels persist three to five weeks The normal lymphocytes are sharply contrasted to the atypical and abnormal mononuclear elements found in infectious mononucleosis and to the lymphoblasts in leukemia Clinical signs and symptoms may be so mild as to escape attention or onset may be marked by vomiting irritability fever abdominal signs and symptoms and occasionally signs of involvement of the nervous system The abdominal signs may be so marked as to suggest acute surgical condition Infection of the upper respiratory tract is the most common finding Significant physical changes such as lymphadenopathy and a palpable spleen are not

(6) J A M A 125 342 349 J 3 1944

the five cases of agranulocytosis showed a striking lack of neutrophil granulocytes (polymorphonuclears metamyelocytes and myeloblasts) but in four there was persistence of promyelocytes and myeloblasts Autopsy and examination of marrow by sternal puncture in three cases showed distinct increase in these immature cellular elements This corresponds to the findings of Kracke and shows that maturation arrest may be found in secondary agranulocytosis just as in the idiopathic types

Pentnucleotide appears to be effective in this type of agranulocytosis provided treatment is not too long delayed

Treatment of Agranulocytosis with Sulfadiazine Norman Nixon John F Eckert and Kendall B Holmes[8] (M C U S A) report three cases of agranulocytosis developing in the course of therapy with sulfadiazine in which the successful outcome was in their belief due to subsequent administration of sulfadiazine.

CASE 1 — Aviation cadet 26 with scarlet fever received moderate amounts of sulfadiazine and was afebrile from the seventh to eleventh hospital day On the eleventh day fever and a scarlatiniform rash recurred The white blood cell count was 6 800 with 6? per cent polymorphonuclear leukocytes Four days later temperature was normal again but the white cell count had dropped to 3 550 with 72 per cent polymorphonuclears Sulfadiazine was discontinued on the fifteenth day after a total of 58 Gm was given During the next two days the white cell count dropped to 1 600 with 13 per cent polymorphonuclears Liver extract pentnucleotide and ascorbic acid had no effect since there was a continuous fall in all white cell elements The eighteenth hospital day fever rose again and sore throat and a cough with mucopurulent sputum appeared In view of imminent death from the overwhelming infection treatment with sulfadiazine was resumed on the eighteenth day The sodium salt was given intravenously in amounts sufficient to raise the blood concentration to 20–25 mg per cent and administration of convalescent scarlet fever serum was begun During the first three days of this treatment the condition remained critical fever was high ulcerations appeared in the throat and at the anus red blood cell count dropped from 5 100 000 to 3 750 000 hemoglobin content fell

(8) Am J M S 06 713 2 D mb 1943

seems advantageous to group them separately from the other dyscrasias which are characterized by various degrees of marrow depression In the second group the initial depressant effect is on the leukopoietic tissues leading to granulocytopenia and agranulocytosis in the peripheral blood often manifested soon after the first injections of arsphenamine and reversible if no more injections are given Depression of megakaryocytes and the erythroblastic series on the other hand only develops as a rule after a considerable number of injections and the dyscrasia may not be found until weeks or even months after the last injection Ferguson s first five cases demonstrated early onset of agranulocytosis average number of injections given being five and average dose 2 1 Gm In the sixth case marrow damage was more extensive affecting the megakaryocytes and red cell precursors as shown at autopsy The hematologic picture was therefore that of acute aplastic anemia Symptoms did not begin until six to seven weeks after beginning antisyphilitic therapy

Changes in the peripheral blood in the first five cases were not essentially different from those found in cases of agranulocytosis secondary to aminopyrine or other drugs or cases of idiopathic agranulocytosis In the three patients who recovered percentage of monocytes in white cells was high When first seen these patients showed a definite increase not only in percentage but also in absolute number of monocytes present in contrast to the relatively low monocyte count observed in the fatal cases

Marrow findings varied considerably Even when the peripheral blood picture was that of aplastic anemia (granulocytopenia thrombocytopenia and erythrocytopenia) the marrow may not be truly aplastic but may show only a decrease in mature elements In other cases the marrow is hypoplastic or aplastic Custer stated that cases of granulocytopenia from arsenicals do not show the well marked proliferation of myeloblasts found in cases of idiopathic agranulocytosis with maturation arrest The marrow in

LEUKEMIAS

Action of Specific Stimulators on the Hemopoietic System Franklin R Miller and D I Turner (Jefferson Med College) describe lesions induced in guinea pigs by administration of partially purified extracts and fraction of extracts obtained from urines of patients with acute and chronic lymphoid myeloid and monocytic leukemia lymphosarcoma and Hodgkin disease

Animals given the active principle from the urine of patient with chronic myeloid leukemia exhibited organ change similar to those found in human chronic myeloid leukemia Identical changes were obtained in animals given *extract from patient with acute myeloid leukemia the* acute nature of the disease was not transferred Animals given extracts from patient with chronic lymphoid leukemia showed changes similar to those found in human chronic lymphoid leukemia The same histologic change were obtained with extract from patients with acute lymphoid leukemia except that the lymphoid hyperplasia and metaplasia in nonlymphoid organ were somewhat greater than in the animals given extracts from chronic lymphoid leukemia To a lesser degree lymphoid hyperplasia and pictures simulating lymphoid leukemia were obtained with *extracts derived from patients with lymphosarcoma*

The changes produced in animals with extracts from patient with monocytic leukemia were neither lymphoid nor myeloid The liver showed some perivascular infiltration by small round cells similar to lymphocytes some of the infiltrations containing many eosinophils The spleen contained many large cells with foamy cytoplasm many fibroblasts and a few multinucleated giant cells The lymph nodes were somewhat enlarged and showed changes similar to those in the spleen The bone marrows of all animals were hyperplastic with increase of megakaryocytes The same finding were obtained with extracts *from patients*

(9) A J M S 206 146 158 Aug 1943

from 16 4 to 11 8 Gm per cent and jaundice developed. Total white cell count varied from 200 to 310 all lymphocytes The first suggestion of recovery of the bone marrow occurred the fifth day of sulfadiazine therapy thereafter there was a rapid rise in all white blood element and four days later there was no evidence of blood dyscrasia The authors believe that the drug was the primary factor responsible for the agranulocytosis

The second and third case occurred in patients with virus pneumonia who were likewise given moderate doses of sulfadiazine before granulocytopenia was noted Although sulfadiazine was the probable factor in causing the agranulocytosis subsequent administration of the same drug plus convalescent human serum resulted in ultimate recovery

On the basis of this experience the authors believe that the patient with agranulocytosis regardless of etiology should not be deprived of the most effective means of combating complicating sepsis but should be given one of the sulfonamides preferably sulfadiazine in large doses until the temporary depression of the bone marrow is overcome and the normal protective mechanisms are again functioning

[illegible] to interpret the success of this heroic h m path the value of chemotherapeutic agents in controlling the infection [illegible] agranulocytosis or acute leukemia has been shown by other However it has been demonstrated that in agranulocytosis is due to aminopyrine readministration of the drug after an interval of cure [illegible] prompt recurrence of the leukopenia In explanation of the paradoxical result reported by Nixon and his associates two possibilities are suggested First the agranulocytosis was not due to the sulfadiazine This cannot be denied but the chronology is at least consistent with the authors belief that the sulfadiazine was the etiologic agent Second the sulfadiazine though causing the agranulocytosis prevented its fatal effect secondary infection until the initial sensitivity or susceptibility of the granulocytes to the drug had disappeared or even been entirely abolished It would be interesting to readminister sulfadiazine to these patients However in case of another infection they should be given another sulfonamide which would have been a more logical but less interesting procedure in the first place [illegible]

macrocytic hyperchromic anemia Leukocyte differential blood pattern and platelets were not appreciably altered There was quantitative decrease in the number of marrow cells while *quantitatively the bone marrow was not changed* The patient was given thyroid extract and for the next four years she was free from preoperative symptoms She then experienced recurrence of headache and dizziness and hemoglobin had risen to 17 Gm and erythrocytes to 7 800 000 Symptoms were relieved by repeated venesections Since then she has taken thyroid intermittently and has been able to pursue routine life

Three cases of erythroleukemia were studied All patients had increased hemoglobin erythrocyte and leukocyte values and immaturity of granulocytes After removal of the thyroid two patients responded with a considerable depression of hemoglobin and erythrocytes The third patient did not show much change in hemoglobin and erythrocyte values despite the existence of myxedema Two of the three had macrocytic and hyperchromic anemia Postoperatively *all three showed progressive leukocytosis and immaturity* of granulocytes many normoblasts and a variable change in the number of platelets In one patient removal of the thyroid induced a megakaryocytic crisis followed later by *normal platelet counts*

In a case of chronic myeloid leukemia followed for a year after thyroidectomy hemoglobin and erythrocyte values decreased progressively and within 10 months were about half the initial counts Mean corpuscular volume increased from 93 to 103 cu μ Total white blood cell count dropped from 145 000 to 90 000 immaturity increased In the bone marrow myeloid immaturity increased and erythroid and megakaryocytic elements were greatly reduced

In a man with chronic lymphatic leukemia under observation for two years after thyroidectomy hemoglobin and erythrocyte values were reduced and total white blood cell count increased from 150 000 to 400 000 with no essential change in differential pattern Bone marrow was unchanged.

A gastric analysis was performed in three cases before thyroidectomy and *after myxedema* and *no changes in* acidity were noted In all cases blood cholesterol values increased after the operation Two of the patients exhibited symptoms of postoperative tetany

with Hodgkin s disease except for a more definite trend toward lymphoid stimulation Animals given equal weights of lymphoid and myeloid stimulating fractions simultaneously showed changes resembling those obtained with urine extracts from patients with Hodgkin s disease or monocytic leukemia

Although a variety of urinary sources were used only two substances produced the histologic changes described here the myeloid and the lymphoid stimulating substance The authors assume that these two substances have reciprocal action the myeloid fraction stimulating myelopoiesis i e proliferation without maturation and inhibiting lymphopoiesis thus bringing about maturation of lymphoid cells The lymphoid substance brings about maturation of myeloid cells by inhibiting proliferation Normally the action of the two substances is balanced The acute forms of leukemias may be explained by deficiencies of one or *the other maturing substance the chronic forms* by exces of the stimulating and normal amount of maturing sub stance aplastic anemia by deficiency of both factors and Hodgkin s disease and monocytic leukemia by excess of both substances If this theory is correct it would suggest the advisability of replacement therapy for human leukemia

Effect of Myxedema on Hemopoiesis in Leukemia and Related Disorders Jerome T Paul Louis R. Limarzi and Lindon Seed (Univ of Illinois) studied the effect of thyroidectomy and subsequent myxedema in cases of polycythemia vera erythroleukemia chronic myeloid leukemia and chronic lymphatic leukemia

A previously reported case of polycythemia vera has been followed for seven years Within three months after thyroidectomy symptoms of myxedema appeared and within two years the patient presented the full picture of hypothyroidism. Th blood picture had changed markedly Hemoglobin erythrocyte and hematocrit values dropped to less than half of preoperative values Total blood volume decreased from 10 706 to 3 790 cc the mean corpuscular volume increased to 103 7 cu μ and the mean corpuscular hemoglobin to 36 1 μμg indicating

(1) Am. J M Sc 06 6 5 630 Nov mb 1943

wer scattered over the entire body There was a large hematoma on the left che t and an ulcer over the mid dorsal spine surrounded by an ecchymotic red and indurated area There were a few purpuric spots on the extremities Removal of the plaques left a persistently bleeding surface Blood count showed 5 9 Gm hemoglobin 2 270 000 red blood cell 72 500 platelets and 23 000 white blood cells per cu mm with 51 per cent polymorph nuclear leukocytes 32 per cent lymphocytes 5 per cent monocyte 1 per cent eosinophil 2 per cent basophils 6 per c nt metamyelocytes 2 per cent myelocyt s and 1 per cent premyelocytes There were many macroblasts and normobla t Bleeding time was over 30 min and coagulation time 2 min 50 ec

She was given transfu ion a total of 890 cc The kin l ions were treated with gentian violet solution and heat and gradually improved but the eschar when removed left a per si tently bleeding surface and the neck never entirely cleared The pleen continued to enlarge and the purpuric pots increa ed in number Inguinal adenopathy developed during the last two weeks of life and her color became greenish Ten days before death she had a cerebral hemorrhage with bulging fontanel ptosis of the left eyelid and opisthotonos The blood picture remained about the ame except for a drop in platelet count to around 35 000 per cu mm Autopsy showed many eo inophilic myelocytes and undifferentiated toxic cells in the bone marrow lymph node and spleen The germinal center were absent from the spleen The uperficial cornified layer of the skin was missing and the basal layer greatly thickened There were hemorrhage throughout all viscera cerebral hemorrhage and edema ubarachnoid bleeding subdural hema toma and myocardial hem rrhage Final diagnosis was mye logenou leukemia cerebral hemorrhage and hemorrhages in all viscera

Of the 20 cases in the literature 16 were myelogenous 3 lymphogenous and 1 que tionable in type

Leukemia and Pregnancy Joseph L McColdrick and Warren A Lapp (King County Hosp Brooklyn) re p rt a case and review the literature

W man 31 pregnant t the eighth time tated that 1 r previously a diagno i f chr nic myelogenous leukemia h l been made and he had received two x ray treatments to th spleen since She had no t xic symptoms throughout preg n nc xcept f r a face ra h On admis ion the spleen filled

4 Am J Ob t & Gy 4 11 18 N mbe 1943

Metabolism of Pyruvate by Normal and Leukemic White Cells Jules C Abels Florence L Jones Lloyd F Craver and C P Rhoads (Memorial Hosp New York City) used for their study white cells obtained from normal adults and from patients with chronic leukemia with acute infections and polymorphonuclear leukocytosis and with chronic pulmonary tuberculosis

From 65 to 101 per cent of the thiamine in both normal and leukemic white cells exists as co-carboxylase Nevertheless those enzyme systems known to utilize co-carboxylase as a coenzyme could not be demonstrated in either the normal or the leukemic cells Qualitative and quantitative differences have been observed for utilization of pyruvate by normal and leukemic white cells The normal cells apparently utilize less pyruvate and usually convert a greater proportion of that compound to lactate than do the leukemic cells This abnormality of the neoplastic cell probably is not due simply to their apparent youth

Congenital Leukemia. Frank S Cross (Lansing Mich) reports two cases and reviews 20 from the literature The second case was of additional interest because of unusual skin manifestations and is given here

Girl born Nov 7 1942 was admitted Dec 22 1942 and died Feb 17 1943 She was the only child of Irish parents was born by normal spontaneous vertex delivery at full term after normal gestation and had a birth weight of 7 lb 6 oz At birth she had heavy crusty coating of vernix caseosa(?) which could not be cleaned off the neck axillae and groin These places became excoriated and infected and large yellow plaques of crustlike scab formed Subcutaneous hemorrhage and bleeding from the bowel were present at birth She was given vitamin K and 12 intramuscular injections of blood She took feeding well and gained weight Abscesses and ecchymoses formed at several points of intramuscular injection and bloody stools continued There was a systolic murmur over the entire precordium not transmitted Liver spleen and cervical glands were palpable There were a few petechiae on the hard palate The scalp was dry and scaly Many petechiae

(2) Cancer R 4 149 152 March 1944
(3) J Ped 24 191 194 February 1944

which they failed to recover An acute exacerbation of the leukemic process has been noted frequently following parturition In general however the course of leukemia was not greatly influenced by gestation Autopsies on leukemic women have frequently shown extensive leukemic infiltrations in the genital tract especially the ovaries and uterus No leukemic child has ever been delivered of a leukemic mother the placenta probably acting as a barrier

Regarding treatment of pregnant leukemic patients most authors agree that the shock of interruption is just as great as that of parturition Interruption may be justified in terminal cases to save a viable infant Arsenic in treatment of chronic leukemia associated with pregnancy seems to be the most rational procedure

Acute Leukemia Complicating Pregnancy with Autopsy Findings in the Fetus is reported by H S Applebaum (Mount Sinai Hosp Cleveland)

Primipara 29 3½ months pregnant complained of pain in buttocks and left abdomen examination revealed nothing abnormal and the pain was attributed to the pregnancy She was given liver iron and vitamins Three months later examination showed enlarged lymph nodes cough anemia and weakness Blood examination indicated myeloid leukemia of great severity Three blood transfusions produced prompt improvement Three weeks later all symptoms had reappeared with greater severity Irradiation and transfusions again caused prompt improvement but despite treatment the course was rapidly downhill Cesarean section was performed to save the child and relieve the patient by terminating the pregnancy The fetus was found dead and the mother died a few hours later

The fetus was about 8½ months old Probable cause of death based on anatomic examination was subarachnoid hemorrhage hemorrhages in both cerebral hemispheres and atelectasis No sign of leukemia was found confirming the belief that a leukemic mother does not transmit the disease to her offspring The fetus might have been saved by an earlier operation but this was opposed in the belief that an operation would kill the mother

(5) Oh Stat M J 40 536 5 J 1944

the entire left side of the abdomen extending down almost to the iliac crest it was solid firm and not tender There was no lymphadenopathy Blood study showed red cells 3,200 000 hemoglobin 55 per cent white cells 250 000 with 40 polymorphonuclears 10 myeloblasts 25 metamyelocytes 15 myelocytes and 10 lymphocytes On the day of admission she delivered spontaneously a stillborn normally developed infant Blood loss was minimal She had septic postpartum temperature and was given sulfathiazole She was un-co-operative refused many medications and food and was discharged in seven days on her own request Visited later at her home by a nurse she was found to be doing her household duties.

The coexistence of pregnancy and leukemia is rare. The authors collected 111 cases from the literature of which only 79 were suitable for statistical purposes Of these 34 were acute cases In 75 cases leukemia developed prior to or during pregnancy Of the acute cases 17 were myelogenous 9 lymphatic 2 hemocytoblastic and the rest unclassified In all but two leukemia developed after onset *of pregnancy The disease was most common in primiparas* and uniparas and began more often in the seventh month of gestation than at any other time Average age at onset of leukemia was 28 04 Life expectancy after onset was 10 weeks (average) Maternal mortality was 100 per cent Fetal mortality was 60 per cent The outlook was more favorable in chronic leukemia 41 were myelogenous and 3 lymphatic Average age at the time of onset was 30 63 It occurred most often in multiparas 51 3 per cent had *chronic leukemia longer than one year prior to pregnancy* Maternal mortality was 36 5 per cent fetal mortality 16 4 per cent In 4 of the 79 cases leukemia developed post partum

Leukemia seems to predispose to spontaneous induction of premature labor Of 49 cases of acute and chronic leukemia in which pregnancy was allowed to progress premature labor developed in 21 Only three fatal hemorrhages during or after delivery occurred in the 75 cases Several authors have observed that their patients withstood parturition but shortly thereafter went into collapse from

Hodgkin's Disease This study by Henry Jackson Jr and Frederic Parker Jr (Harvard Univ) is based on material collected over a period of years from Boston City Collis P Huntington Memorial and Pondville hospitals and from private practice

General Considerations —Hodgkin s disease may be divided into three types paragranuloma granuloma and sarcoma on the basis of two feature (1) presence in each of so called Reed Sternberg cells and (2) transformation with the passage of time of one type of the disease into another Hodgkin s paragranuloma bears little or no resemblance to a true tumor either in histologic picture or in clinical course The often scattered Reed Sternberg cells lymphocytic infiltration with or without destruction of the lymph follicles and complete lack of invasiveness all indicate an infectious process as do the comparatively benign course and the fact that in almost all cases the disease starts in the lymph nodes of the neck to which the causative agent may have gained access through the pharynx Hodgkin s granuloma likewise appears to be an inflammatory process rather than a neoplasm in view of the fact that the Reed Sternberg cells are frequently scattered isolated and often separated widely by cells of other types On the clinical side the irregular bouts of fever seldom absent in the more advanced stages and often seen early in the course especially the relapsing Pel Ebstein fever type marked anemia in absence of bleeding or widespread invasion of the marrow the polymorphonuclear leukocytosis and the prominent and persistent tachycardia all are more characteristic of an infectious process than of a tumor Hodgkin s sarcoma has all the characteristics of a true neoplasm The uniformity of the cellular constituents the aggressive invasive nature of the process the extremely short duration of life and the not uncommon finding of a large destructive tumor with comparatively few metastases all favor this concept So also does the fact that the

( ) N w E gla d J M d 30 1 8 J 6 31 35 44 J ly 13 1944

Reaction of Leukemic Patients to Sulfonamides is demonstrated by L I Amidon (Univ of Vermont) in four cases of lymphatic leukemia

CASE 1—Woman 36 with acute lymphatic leukemia was given sulfanilamide 1 Gm every four hours for three days White blood cell count dropped from 89 000 with 98 per cent lymphocytes on admission to 6 200 with 95 per cent lymphocytes Four days later with white cell count 41 800 sulfathiazole in 1 Gm dose every four hours was started but because of the prolonged leukopenia it was discontinued the fourth day During hospitalization the patient s condition improved from a moribund state to that of comparative health On discharge one month after admission white cell count was 7,200 with 6 per cent lymphocyte and 44 per cent neutrophils Four weeks later she was hospitalized elsewhere again a dramatic drop in white cells occurred after sulfathiazole was started Eight days after medication was begun the patient died

CASE 2—Man 76 with white blood cell count 306 000 and 86 per cent lymphocyte showed symptoms of vascular collapse after the second dose of 1 5 Cm sulfathiazole The drug was stopped then later readministered in doses of 0 5 Gm three times daily Only a slight change in the hematologic picture occurred after a total dose of 6 Gm sulfathiazole The patient died one week after admission

CASE 3—Woman 39 with acute lymphatic leukemia rallied from a nearly moribund state after sulfathiazole was given Total dose was 9 Gm It is felt that the drug should have been continued Three weeks after admission the patient died of pneumonia

CASE 4—Man 68 with acute lymphatic leukemia was in extremis on admission He responded so well to sulfanilamide that he was able to return to his job as janitor Sulfadiazine had no effect on the white blood cell count He died elsewhere a few months later

It appears that certain of the sulfonamides produce a sudden drop in the circulating lymphocytes in lymphatic leukemia This does not occur in myelogenous leukemia That this is not a toxic effect of the sulfonamides is indicated by the suddenness of the response and the clinical improvement that usually follows

[This is not to be regarded as a satisfactory method of treating lymphatic leukemia —Ed]

(6) J Lab & Cl Med 8 1191 1695 November 1943

aged or elderly Eighty per cent of the 51 patients in the pre ent series were over 40 and n ne was under 20 Fifty one per cent were men

Pathology.—Apparent primary site in 26 cases of Hodgkin s paragranuloma were cervical lymph nodes in 23 inguinal lymph nodes in 2 and axillary lymph nodes in 1 Diagno is is based on presence in the involved nodes of Reed Sternberg cells and absence of fibrosis or necrosis In certain cases the presence of fairly numerous eosinophils and fibrin is evidence that a transformation into the granu lomatous form is impending there are transitional types in which it is difficult to di tinguish between paragranuloma and granuloma As long a the pathologic process remains unaltered prognosis is relatively good

Hodgkin s granuloma is characterized by presence of Reed Sternberg cells pleomorphism eosinophils necrosis and fibrosis It may involve any organ of the body except the central nervous system proper Autopsy studies on 59 cases showed that the retroperit neal and para aortic lymph nodes are most frequently the primary site of the disease followed by other lymph nodes and the stomach or intes tines Clinical observations however indicate that the cer vical nodes are usually the primary site Possibly the favorable response of the more superficial nodes to x ray therapy and the difficulty of recognizing involvement of the deeper nodes and internal organs during life account for the apparent discrepancy Tuberculosis is frequently associated with this type of Hodgkin s disease The two processes may exist side by side in the same organ and although grossly they may be confused histologic charac teristics of each are definite Involvement of lymph nodes is usually widespread and of fairly uniform distribution The spleen was involved in 75 per cent of cases and the liver in 53 per cent Involvement of bones occurred in 61 per cent of cases in which the bones were examined

Hodgkin s sarcoma is characterized by presence of typi cal Reed Sternberg cells scattered among cells that are

disease is commonest in the sixth and seventh decades and its occurrence is extremely rare in persons under 30

If the aforementioned concept is correct, etiology of the paragranuloma is identical with that of the granuloma The granulomatous form does not appear for a time owing to relative immunity of the host or to lack of virulence of the agent Hodgkin s granuloma is frequently complicated by tuberculosis The coexistence of the two diseases was found in 20 per cent of the present series The fact that both can be found in one patient or even in the same organ seems to indicate the lack of identity of the two diseases for it is highly improbable that a host would react in two entirely distinct ways to the same micro organism Culturing of a large number of lymph nodes yielded in no instance a positive culture of Mycobacterium tuberculosis in material removed from Hodgkin s granuloma In a considerable number of cases of Hodgkin disease a small gram positive strictly anaerobic gas forming bacillus was grown on chopped meat broth it was however cultured also from cases with other forms of lymphoma carcinoma, tuberculosis and chronic inflammatory lymph nodes No relation of this organism to Hodgkin s disease could be demonstrated by agglutination skin tests and animal inoculations Portions of lymph nodes used for culturing of tubercle bacilli were inoculated into rabbits guinea pigs and pigeons with negative results Tuberculin testing of patients with Hodgkin s granuloma revealed a definite anergy to both human and avian tuberculin It is concluded that the etiology of Hodgkin s granuloma has yet to be discovered

It is tentatively concluded that Hodgkin s granuloma accounts for approximately 0 25 per cent of deaths in a general hospital Age incidence in the 237 cases of the present series was evenly distributed from earliest childhood to the age of 70 Seventy per cent were in males Hodgkin s granuloma occurs more frequently in members of the same family than can be accounted for by chance alone Hodgkin s sarcoma occurs chiefly in the middle

aged or elderly Eighty per cent of the 51 patients in the present series were over 40 and none was under 20 Fifty one per cent were men

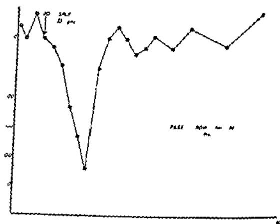
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Hodgkin s sarcoma is characterized by presence of typical Reed Sternberg cells scattered among cells that are

probably extremely anaplastic forms of Reed Sternberg cell It behaves as a true tumor is highly invasive and malignant and may involve any organ including the central nervous system proper The organs most frequently involved in 27 cases studied at autopsy were liver gastrointestinal tract pancreas bones and lungs

Further Studies of Platelet Reducing Substances in Splenic Extracts Troland and Lee in 1938 reported that acetone extracts of spleens from patients with idiopathic



F 59—Pl t l t d p ff t of pl a c e t t fro se f d p th th n bop e p pu a

thrombopenic purpura produced a marked transient lowering of platelets when injected into rabbits Some subsequent workers confirmed these results others were unable to reproduce them Ko c and Boyer in 1940 reported definite platelet lowering effect of spleen extracts from purpura patients confirming Troland and Lee s results In 1940 Paul further demonstrated a platelet depressing substance Eugene P Cronkite (Stanford Univ) now reports similar results He obtained an identical action with acetone

(8) J L b & Cl n M d 8 5 6 J ry 1944

extracts of a spleen from a patient with chronic malignant neutropenia without evidence of thrombopenia

Troland and Lee demonstrated that potency of the extract diminished with heating. Cronkite suggests that further work be done controlling all phases of extraction to determine whether such factors as oxygen, presence of some metal as catalyst or other minor chance happening may inactivate thrombocytopen. Furthermore, normal platelet counts of rabbit have not been definitely enough

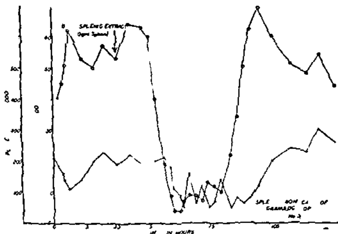


Fig —Pl t l t-dep g ff t f plen tract f m case of h mal g eut pe

established to permit acceptance of reports confirming existence of the platelet lowering effect of these extracts. Thrombocytopen when demonstrated has been considered a specific substance occurring in cases of idiopathic thrombopenic purpura. It was not demonstrable in normal spleens or in spleens from patients with leukemia, Banti's syndrome, aplastic anemia, congenital hemolytic jaundice and splenic vein thrombosis. However the most potent effect

reported by Cronkite were obtained with extract from a patient with idiopathic malignant neutropenia with thrombocytosis. Indefinite responses were obtained with extract of a tuberculous spleen from a patient whose condition clinically resembled idiopathic purpura.

There is no doubt that platelet lowering substances may be extracted from certain spleens. The next step should be purification and identification of the effective substances.

PURPURA AND TELANGIECTASIA

The second article in this section serves to emphasize the important therapeutic point that acute thrombocytopenic purpura may be a manifestation of the onset of various acute infections, frequently meningococcemia or gonococcemia. For these chemotherapy may be v rounys m is -l d l

***Thrombocytopenic Purpura** is discussed* by Horace Evans and Kenneth M. A. Perry on the basis of 75 cases observed at London Hospital between 1927 and 1938 and followed up until the outbreak of war. Sex incidence is about even before puberty; thereafter there are five females to one male. There is a peak in early adult life and again during the menopause.

In the prepuberal group of 30 patients 5 could not be traced, 5 died, 15 had no symptoms and no thrombocytopenia at the end of the observation period and in 6 the disease persisted, 1 of these dying a year after splenectomy. *Three died of subdural hemorrhage, one of hemoptysis* and one of septic meningitis. Presenting symptoms were bleeding from gums in 8 cases, epistaxis in 10, generalized purpura and ecchymoses in 16, hematuria in 4, hematemesis in 3, hemarthrosis in 1, retinal hemorrhage in 1, subdural hemorrhage in 3, hemoptysis in 1. In nine instances the red cell count was below 2,000,000. The platelet count usually falls during an exacerbation to below 10,000 and bleeding time is prolonged to 30 minutes and more. Most cases had moderate leukopenia with relative lymphocytosis.

In the postpuberal group were 38 females. The disease is much more severe in women than in children; mortality

(9) Lan t 410 413 O 1943

for the former being 40 per cent and the likelihood of spontaneous recovery small (one case) The possibility of spontaneous cure in childhood is stressed by the fact that only one woman dated her symptoms before the age of 15 The symptoms in this group were similar to those in children with addition of menorrhagia Three patients had retinal hemorrhages and one each labyrinthine hemorrhage jaundice jacksonian epilepsy and aphasia One patient showed striking improvement during pregnancy and thyrotoxicosis was associated with the purpura in four suggesting a possible endocrine origin of the disease In the seven males in the postpubertal group symptoms were much less severe two recovered spontaneously and one died of subdural hemorrhage

Secondary thrombocytopenic purpura was seen during the same period of observation in four cases of leukoerythroblastic anemia five cases resulting from N A B two from quinine and two from phenobarbital None of these is included in the total 75 cases of idiopathic purpura

Splenectomy was highly successful in the males of the prepuberal group resulting in immediate and permanent cure in all five patients operated on In the females however the only patients who showed persistence of the disease were the four who had splenectomy In the female postpuberal group splenectomy carried an operative mortality of 23 per cent with no certainty of cure Cure resulted more often in women over than under 40 However splenectomy may be a life saving measure and is sometimes advisable in the hope of preventing subdural hemorrhage In the male postpuberal group there were two splenectomies with cure

[This article emphasizes the unfortunate fact that splenectomy in thrombocytopenic purpura is not as is sometimes assumed a reliable means of cure It is however the only positive means by which benefit or cure may be expected —Ed]

Purpura Fulminans (Waterhouse Friderichsen's Syndrome) A case with recovery is reported by Stephen D Peabody (Newburyport Mass)

(1) New England J Med 229 934-936 Dec 16 1943

Girl 19 had the day before admission slight fever malaise and general discomfort In the evening she vomited at times and complained of generalized aching pains On admission there were a generalized blotchy petechial skin eruption and a few petechiae on the buccal and pharyngeal mucosa and on the sclerae and conjunctivas There was marked tenderness over the long bones and joints Ankle jerks were absent The Rumpel Leede phenomenon was not present Blood pressure was 60/40 pulse 150 and rectal temperature 98 1 Initial blood examination showed hemoglobin 98 per cent red cells 5 300 000 white cells 41 000 with 72 per cent nonsegmented neutrophils 22 per cent segmented neutrophils 3 per cent lymphocytes and 3 per cent monocytes Bleeding time was 5 minutes clotting time 3½ minutes prothrombin time 19.5 seconds

The patient was placed in shock blocks and given 500 cc plasma without effect on the blood pressure She was then given 5 Gm sodium sulfadiazine intravenously and 2 Gm sulfadiazine every four hours by mouth Twenty cc adrenocortical extract was given intravenously followed by 2 000 cc normal saline One hour after administration of the adrenal extract blood pressure had risen to 80/60 but the extremities remained cold and numb and pulse was 160 and weak The evening of admission facial edema was evident She was taken off shock blocks and given 10 cc cortical extract twice during the night

On the second hospital day rectal temperature was 99 F blood pressure 90/50 and pulse 150 She was restless and delirious her head retracted and there was definite nuchal rigidity Spinal puncture revealed cloudy thickened fluid pressure 195 mm 1 000 red cells and 7 550 white cells glucose 32 8 mg per cent and sulfadiazine level 11 6 mg per cent no organism could be cultured A blood culture showed meningococci

On admission blood chloride level was 514 mg per cent glucose 94 mg and nonprotein nitrogen 116 mg Urinary output in the first 24 hours was 15 cc despite the 4 000 cc fluid intake Edema of the subcutaneous tissues developed and urine showed heavy trace of albumin and many red cells She was given 105 cc polyvalent antimeningococcus serum the second day of hospitalization The third day she had generalized edema was unable to hear and had bilateral internal strabismus Systolic pressure had risen to 140 and pulse was 90 From then on there was gradual improvement The only complica

tions were hydrarthrosis of knees and elbows the sixth day after administration of the meningococcus serum and deep pressure sores over some of the petechial eruptions on the heels and buttocks

Amino Acids and Blood Clot Retraction. Diminished blood clot retraction is usual in patients with thrombocytopenia and often in those with hypoprothrombinemia Kabinowitz reported that 150 mg cysteine added to normal blood in vitro would abolish clot retraction for more than 24 hours and that 150 mg methionine cystine or glycine would neutralize the effect of cysteine with resulting complete retraction of the clot within three hours He also reported similar increases in degree of blood clot retraction after addition of these amino acids to samples of the blood of five patients with essential thrombocytopenic purpura Oral administration of methionine (5–8 Gm daily) to these patients restored normal clot retraction and controlled spontaneous bleeding Subsequently Rabinowitz used 5 Gm methionine in 1 000 cc of 5 per cent glucose solution intravenously in several cases of thrombocytopenic purpura with most gratifying results P M Aggeler and S P Lucia (Univ of California) attempted to repeat these experiments Personal communication from Rabinowitz revealed that cysteine hydrochloride and not cysteine was used in the experiments

In vitro studies of blood of normal subjects showed that cysteine hydrochloride in the concentrations necessary to inhibit clot retraction strongly acidified the blood hemolyzed erythrocytes coagulated plasma proteins and completely inhibited formation of fibrin None of these effects was noted with glycine cystine or methionine furthermore they did not counteract any of the effects of cysteine hydrochloride In vitro studies of the blood of six patients with thrombocytopenia showed that blood clot retraction was not significantly altered in any case following addition of cystine glycine or methionine Oral administration of

( ) S g y 15 48 490 M h 1944

glycine and intravenous administration of methionine to three patients with thrombocytopenic purpura did not improve blood clot retraction or alter the frequency or severity of spontaneous bleeding in any

[Another therapeutic agent allegedly effective in thrombopenic purpura is orally administered p ctin It would be well if this claim could be proved or disproved in the near future—Eds]

Hereditary Hemorrhagic Telangiectasia. Karl Singer and William Q Wolfson (Middlesex Univ Waltham Mass) report an analysis of capillary heredopathies based on study of a family in which typical lesions of hereditary hemorrhagic telangiectasia and positive tourniquet tests were present in all members examined

Woman 80 complained of repeated spontaneous epistaxis for 40 years Cauterization of the nose seven years previously gave relief for six months Red spots had been on the ends of fingers and oral mucous membranes for 30 years History was otherwise negative except for episodes of acute arthritis 20 years previously The red spots were typical lesions of telangiectasia While under observation temperature varied from 97 to 98 6 F and pulse from 70 to 80 Several blood pressure determinations showed 140 60 Blood studies showed red cells 4 100 000 3 per cent reticulocytes hemoglobin 90 per cent white cells 9 100 with 5 per cent staff cells 67 per cent neutrophils 21 per cent lymphocytes 4 per cent monocytes and 3 per cent eosinophils color index 1 08 Hematocrit reading was 38 mean corpuscular volume 92 cu microns platelet count 220 000 Clot retraction was normal Prothrombin time was 20 seconds (normal 18 seconds) by the Quick method bleeding time 2 minutes (Duke method) clotting time 4 minutes (Lee White method) and sedimentation rate 9 mm in 1 hour (Wintrobe method) The tourniquet test was distinctly positive

Investigations revealed a strong familial and hereditary tendency to telangiectasia The patient s father had had marked telangiectasia and epistaxis occasionally severe enough to lead to fainting Of her two sons (one died of diphtheria at 2) the older first experienced epistaxis at 22 and was forced to stop playing the trombone because blowing induced the bleeding Typical telangiectasia developed later but bleeding was never as severe as in the mother This son died at 55 of peritonitis Of 66 other members of the family (33 males and 33 females) 8 boys and 8 girls have telangiectasia some

(3) New England J Med 30 637 (4 May 5 1944

either are too young to show the lesions yet In one line telangiectasia was present in the first generation not in the second and third and reappeared in the fourth. A girl of the third generation with telangiectasia married her first cousin of the third generation who did not have telangiectasia two pregnancies resulted in a hypermature stillbirth and an infant with complete spina bifida The association of hereditary hemorrhagic telangiectasia with anomalies of the vertebral column has previously been reported

Only two other members of the family could be examined One had more tendency to bleed from the visible telangiectasias and greater tendency to bruising than the first patient but less epistaxis and the tourniquet test was less positive In the third case with similar findings tendency to bruising was even more prominent and the tourniquet test was the most strongly positive of the three

[Such cases add support to MacFarlan s thesis of abnormal vascularity in all types of purpura See the 1941 YEAR BOOK OF GENERAL MEDICINE p 456—Ed]

Elliptocytosis in Man Associated with Hereditary Hemorrhagic Telangiectasia This combination of two rare anomalies occurring in members of a Jewish family is reported by John B Pentold and John M Lipscomb (London Hosp) Those members of the family showing elliptical red cells also had signs of hemolytic icterus without an increase in fragility Three members showed a slight degree of secondary anemia and one had an increase in red cells Five persons had over 90 per cent of oval red cells The wet film consistently gave higher percentages than the dry film Blood diluted in hyper and hypotonic saline revealed that the absolute number of oval red cells diminished to a minimum about the third or fourth day increasing again later Corresponding to the absolute diminution of oval cells was an absolute increase in cells that appeared to be round indicating that the oval shape could be changed by alteration in the physical character of the medium The total white differential and platelet counts and the coagulation and bleeding times were normal and the Wassermann and Kahn tests were negative in these subjects

(4) Quart J Med 12 1 716 11 1943

With regard to hereditary hemorrhagic telangiectasia four of the members conformed to classic standard and three others showed parts of the syndrome but were young enough to develop the complete picture later One case presented is classic

M n 54 w a first seen in 1934 with a history of epistaxis for years pallor weakness and dyspnea There were small telangiectasias on lips tongue and nostrils and spider like



Fig 61 —D d blood film f hm n e n ed c d from × 640

lesions on cheek br k abdomen arms and under the nails The red cell count was 2 .00 000 hemoglobin 55 per cent Abundant oval red cell were found

The authors assume that the significance of association of elliptocytosis and hemolysis has been ignored in the literature Their own review of the 350–400 reported cases disclosed that 50 (12 per cent) had some signs of hemolysis

HEMOPHILIA AND OTHER VARIETIES OF DEFECTIVE BLOOD COAGULATION

Congenital Fibrinopenia has been described under various titles such as afibrinogenemia, constitutional hereditary fibrinogenopenia of Schonholzer, constitutional fibrinopenia of Risak and pseudohemophilia. The last term was used because of similarity to hemophilia from which it differs, however, in the factors affecting coagulability of the blood. The disease is extremely rare, only six cases having been reported according to Quick, who excludes Risak's four cases because they do not fit into the true classification since there were traces of fibrinogen in the blood. In the opinion of Mariano R. Castex, Alfredo Pavlovsky and Alton o Bonduel (Buenos Aires), Quick's differentiation is not justified, for traces of fibrinogen are also found in these six cases, but in amounts insufficient to form a coagulum. They report a case of congenital fibrinopenia.

I ov 4½ had a history of profuse bleeding on three occasions: circumcision one week after birth, operation for cleft lip at 11 months, and extraction of a molar at 3½ years. On admission blood studies showed 3,590,000 red cells, 70 per cent hemoglobin, 6,800 white cells, 72,000 platelets. No coagulation of the blood was noted on repeated examinations even after 48 hours; on one occasion a small fibrin net was seen, proved to be composed of white blood cells and platelets. In study of the thrombin time after 30 seconds a tiny amount of fibrin was formed on one occasion, but there was no coagulation otherwise. In study of thromboplastin time after 2 minutes and 15 seconds a small fibrin net was formed, but no further coagulation. There was no clot retraction. The Rumpel Leede phenomenon was not present. Bleeding time was not investigated because of fear of hemorrhage. Chemical examination of the blood revealed absence of fibrinogen. Determination of fibrinogen values in the blood of the members of the immediate family h cl e l normal levels and normal coagulation time.

Addition of calcium to either plasma or whole blood of the patient failed to change the incoagulability. After 24 hours a light trace of fibrin formed but not sufficient to induce coagulation. Addition of normal human serum, rabbit thromboplastin or human milk thromboplastin had no effect on coagula

(New York Univ) believe that since the normal values of clotting time vary considerably to determine the actual changes in clotting time of local venous blood of an extremity it would be more reliable to use not the figures accepted as within normal limits but the clotting time of blood drawn at the same time from the normal extremity of the same individual This was done in the present study

The 191 subjects studied comprised four groups Group 1 consisted of 28 normal students who served as controls group 2 of 115 patients with varicose veins of the lower extremities treated with sodium morrhuate group 3 of 36 subjects with untreated varicose veins and group 4 of 7 patients with postoperative venous thrombosis and five with primary acute thrombophlebitis Coagulation time of the blood from the upper and lower extremities was determined in each individual 552 duplicate sets of determinations were made in the 191 subjects in none of which did the difference between findings of two observers exceed 10–20 seconds

The results revealed a slight tendency for venous blood from the lower extremity to clot more rapidly than that of the upper in 60 per cent of the normal individuals An exaggeration of this tendency was found in the blood from varicose veins in 72 and 77 per cent of groups 2 and 3 respectively and in the blood from the lower extremity of 92 per cent of group 4 Taking those cases of all groups in which the blood clotted more rapidly from the lower extremity the magnitude of acceleration was two times greater in varicose veins than the average difference of normal individuals and the maximal difference was five times greater than the maximal difference of the normals in the cases of established thrombophlebitis it was 4½ times greater than the average acceleration of normal subjects and the maximum five times greater

Based on these findings the following questions require further research In regard to varicose veins what change occurs in the diseased leg to cause this acceleration of clotting time as compared with that in the normal extremity?

Does this rapidity of clotting increase with functional impairment of the physiology of the veins? Does it disappear in recumbent position Do varicose veins showing hyper coagulability predispose to postoperative thrombo embolization In regard to thrombophlebitis is the tendency to acceleration of clotting time due to the same alterations as in varicose veins? Does it antedate the formation of thrombus If so may it not be developed into a prognostic sign indicating preventive therapy?

Increased Coagulability of Blood Theo R Waugh and D W Ruddick[1] (McGill Univ) report a test that allows for recognition of accelerated coagulation and apparently indirectly measures the thromboplastin present This is accomplished by controlled deceleration of the process by use of heparin

TECHNIC—Increasing concentrations of heparin are made up in physiologic saline so that 0 5 cc saline contains 0 1 0 2 0 3 up to 0 7 unit of heparin Nine Wassermann tubes are placed in a special rack which can be tilted on a central axis and the tubes are prepared by addition of the heparin solution Test tube no 1 is empty no 2 contains 0 5 cc normal saline and the other seven contain 0 5 cc of the heparin saline solution in increasing concentration One cc whole blood freshly drawn from the arm vein is placed in each tube which is then corked The rack and tubes are gently agitated to insure mixing of blood and fluid The time is recorded and the actual test conducted at room temperature begun The rack is gently tilted clockwise every two minutes to an angle of 70–80 degrees and fluidity of the blood in each tube is noted The end point for each tube is that point at which the blood no longer flows along the side of the tube The time taken for each tube to congeal is recorded on graph paper plotting heparin concentration against time in minutes

This test used on 50 normal adults showed that while there is some variation in different individuals the graphs fall within well defined limits which are established as bounds of normal

The test was then used on a large number of patients under various circumstances Velocity of coagulation was accelerated during uncomplicated bed rest i e in patients

(1) Canad M A J 51 11 1 July 1944

confined to bed who were not seriously ill but were admitted for investigation or for minor surgery. Several persons with acute localized or generalized infections including pneumonia, empyema, peritonitis and abscesses showed a high degree of clockwise rotation of the curve, indicating acceleration of the coagulation process. Tests carried out on patients after operations showed acceleration of coagulation. Three patients with acute exsanguinating hemorrhage showed the greatest degree of acceleration of coagulation, confirming the view that the blood clots more rapidly under such circumstances, owing perhaps to the fact that rapid entrance of tissue fluids into the circulating blood in an attempt to maintain volume raises the content of thromboplastin in the plasma to an extremely high level. Three patients with carcinoma of the cervix tested during x-ray therapy demonstrated a counterclockwise rotation of the curve, indicating slowing of the coagulation process.

Neurologic Complications of Hemophilia. Types of bleeding most frequently seen in patients with hemophilia are hemarthroses, epistaxis, ecchymoses, hematuria and prolonged hemorrhage into or from any lacerated or contused organ or tissue. Hemorrhages into the lungs or gastro-intestinal tract are less common, although bleeding may occur anywhere in the body. The most characteristic site of hemorrhage is into the joints. Lesions of the nervous system are among the most unusual complications of hemophilia. P. M. Aggeler and S. P. Lucia (Univ. of California) present a review of all known instances in which such complications occurred and report on three cases of nervous system involvement seen in the last four years. The lesions in these cases included (1) spontaneous cerebral hemorrhage and chronic arachnoiditis from previous subdural and subarachnoid hemorrhage, (2) paralysis of the left femoral nerve as indicated by marked diminution in sensibility to touch, pain and temperature in the area of skin supplied by the left femoral nerve, and (3)

(8) J. N. & M. t. D. 99:475-500, M y 1944

paralysis of the left femoral nerve as indicated by marked hypesthesia for all qualities white dermatographism and marked diminution of the pilomotor reflex on indirect stimulation and a massive hemophilic pseudotumor of the left ilium

PROTHROMBIN DEFICIENCY

On the Constitution of Prothrombin Armand J Quick (Marquette Univ) presents experimental findings which indicate that prothrombin is composed of calcium and two separable components A and B

Component A disappears from oxalated plasma when stored in a refrigerator presumably it is destroyed by oxidation Concentration of component A is much higher in dog or rabbit than in human plasma Addition of either of the former plasmas after component B has been removed to human plasma reduces the prothrombin time to 9 or 10 seconds (normal 11–12½ seconds) Component A is heat labile and to a certain degree group specific It is stable in native or unmodified plasma whereas in citrated or oxalated plasma it is easily destroyed This suggests that in blood the two components are bound by calcium and are thus protected against external factors such as oxidation

Component B disappears in the plasma of animals poisoned with dicumarol Preliminary studies suggest that a deficiency of vitamin K likewise produces a reduction of component B as was found in a patient with obstructive jaundice It is heat labile and is completely removed from oxalated plasma by aluminum hydroxide This adsorbent does not remove the factor from unmodified plasma thus indicating that when it is combined in the prothrombin complex it is not absorbed Component B is group specific

Decalcifying agents inhibit coagulation of the blood by depressing the calcium ion concentration of the system

(9) Am J Phy 140 212 20 Nov 1 1943

$$\frac{\text{Prothrombin} = \text{A Ca++}}{\text{Prothrombin Ca}} = \text{K}$$

More sodium citrate is needed to suppress the coagulation of rabbit than of human blood

The new concept is of theoretical importance especially in emphasizing that biologic agents may be complexes that are easily dissociated and resynthesized The following practical considerations arise from the hypothesis that prothrombin is a three component complex Little is known concerning the quantitative relationship of components A and B and it seems hazardous to depend on results obtained by high dilution of plasma for quantitative determination of prothrombin It must be assumed that prothrombin which is dissociated in decalcified plasma is on recalcification resynthesized i e components A and B and calcium are recombined The use of plasma treated with aluminum hydroxide may lead in certain experiments to serious errors since this plasma cannot be considered merely as being prothrombin free cognizance must be taken of its content of component A Views on the use of stored plasma for transfusion must be modified. Heretofore such plasma was considered unsuitable for treating hypoprothrombinemia Since stored plasma loses only component A and as only component B is depleted in dicumarol poisoning stored plasma should be as effective as fresh plasma This is of practical importance since in patients receiving dicumarol a hemorrhagic condition that demands an emergency transfusion may develop precipitously With the realization that prothrombin is composed of several factors a clearer and fuller understanding of the hypoprothrombinemias should be attained and a more concise classification should be possible At present all the cases of clinical hypoprothrombinemia appear to be deficiencies of component B Although depletion of component A has been observed only in vitro it is probable that clinical hypoprothrombinemia due to lack of this factor may occur

Prothrombin Deficiency in Biliary Obstruction and Diseases of Liver Freda K. Herbert[1] (King's College Newcastle upon Tyne England) estimated the incidence of prothrombin deficiency by the two stage method in [illegible] cases of obstructive jaundice with serum bilirubin levels over 2.4 mg. per 100 cc. In 68 per cent there was hypoprothrombinemia and in 50 per cent the titers fell below 50 per cent of the normal average. Of 40 cases of liver disease hypoprothrombinemia was found in 68 per cent and in 75 per cent the titers fell below 50 per cent. In some cases hypoprothrombinemia was found when the jaundice was extremely slight. Restoration of the plasma prothrombin level to normal was obtained in some cases of biliary obstruction by treatment with 2 methyl 1 4 naphthoquinone, the treatment failed when there was damage to the hepatic parenchyma. Vitamin K or its analogues were not successful in treatment of hypoprothrombinemia associated with damage to the hepatic parenchyma.

In common with other authors Herbert found that patients with a normal plasma prothrombin before operation may develop hypoprothrombinemia and hemorrhage a few days after operation. Thus a normal prothrombin titer before operation does not exclude the risk of hemorrhage. As far as can be judged postoperative hemorrhage is likely to occur when the plasma prothrombin is 60 per cent or lower.

Idiopathic Hypoprothrombinemia In 1941 Rhoads and Fitz Hugh reported the case of a young white male with a previous diagnosis of atypical hemophilia in which discovery of marked hypoprothrombinemia resistant to treatment with vitamin K required a change of diagnosis to idiopathic hypoprothrombinemia. The patient died as a result of central nervous system hemorrhage. The liver showed atrophy of liver columns but the changes were too slight to be the cause of the low plasma prothrombin. The case of Peard cited by Quick was similar in many

(1) New England J. M. 229:15 Aug 12 1943

respects to that of Rhoads and Fitz Hugh but despite continued bleeding the hypoprothrombinemia responded favorably to vitamin K

Franklin D Murphy and John K Clark (Univ of Penn sylvania) report a case of a youth 18 with symp toms in common with those of Rhoads and Fitz Hugh s patient He had marked hypoprothrombinemia unre pon sive to various preparation f vitamin K The platelet count wa never low enough to account for abnormal bleeding Hemorrhage started early in life and bleeding time was often prolonged Special studies revealed that the plasma fibrinogen was qualitatively defective although this was shown less well in the present than in the other case There were however definite differences between the ca e Coagulation time in the present case was always normal clot retraction good and bleeding usually from nose and gum margins and there was a familial history of bleeding in a female ibling In Rhoads and Fitz Hugh s case *prolonged coagulati n time and poor clot retraction* were pre ent hemarthr sis was common and there was n familial history of abnormal bleeding Despite these differences both ca es should be classified together since in both bleeding was pr bably due to unexplained hypo prothrombinemia

Another significant point i that except for the hypo prothrombinemia the authors case seems to fit into the clas of p eudohemophilia The cause of the hypoprothrom binemia could not be determined Lack of response to vitamin K argued against existence of a deficiency or in adequate absorption of the vitamin Poor utilization of vitamin K by the liver was not probable since liver function test were normal the liver was not enlarged and there was no evi lence of liver disease There were similarities t patients who received overdoses of dicoumarin but n evidence of a toxic agent inducing the hypoprothrom binemia could be elicited The term idiopathic hypo

In the other three prothrombin time became prolonged about the same as when salicylate alone was ingested Five who received 6 mg menadione daily showed protection against prothrombinopenia Two patients received 1 5 mg menadione to each gram of acetylsalicylic acid which had previously induced prothrombinopenia and exhibited complete protection One patient with acute rheumatic endocarditis finally required intravenous administration of ascorbic acid to control the prothrombin time

Generally about 1 mg synthetic vitamin K will counteract *the prothrombinopenia inducing action of 1 Gm* acetylsalicylic acid When fever toxemia and limited nutritional intake complicate the situation adjuvants such as ascorbic acid may be needed This is determined by serial estimations of the prothrombin time a procedure most sensitive and reliable when diluted (12 5 per cent) plasma is used

Treatment of Prothrombinopenia with Water Soluble Menadione *Harry R Litchfield Harris M Rabinowitz* Philip Kavetsky M J Greene and Elsie Kaye (Beth El Hosp Brooklyn) recommend a procedure for taking the prothrombin time smear and red blood cell count at the time of delivery as a safeguard to forestall hemorrhagic disease of the new born and for early diagnosis of erythroblastosis foetalis

Infants with hemorrhagic disease showed marked prolonged *prothrombin time Cord blood* at birth shows a normal prothrombin time and hypoprothrombinemia in the first three days of life The hypoprothrombinemia and associated hemorrhages in the new born were effectively prevented by administration of 0 5 mg water soluble menadione tablet to the mother four hours before delivery Infants delivered from mothers not given menadione can be adequately protected by intramuscular injections *of 1 mg (1 000 units) within 12 hours of delivery* The preparation is more rapidly effective when injected intramuscularly than when given in tablets In cases of ex

ces ne bleeding before the time of delivery a synthetic vitamin K preparation clots the blood after a few hours

There were no toxic effects from either oral administration or injection No tissue damage was discovered from the intramuscular injection the water soluble preparation is more quickly absorbed than menadione in oil solution and insures quicker response The mothers reported a sense of smarting in the area of injection for about five minutes after which all irritation disappeared

Premature infants show a moderately prolonged prothrombin time One premature with asphyxia showed marked prolongation One milligram of the menadione injected intramuscularly caused a rapid rise of prothrombin time in eight days Another premature infant a bleeder was given 1 mg intramuscularly with control of the spontaneous bleeding Intramuscular injection of 1 mg causes a rapid rise of the plasma prothrombin level of new born infants with hypoprothrombinemia whether there is a hemorrhagic tendency or no clinical manifestation of the depressed prothrombin level

Thus the therapeutic value of water soluble menadione is established in hypoprothrombinemia and potential or actual hemorrhage of obstructive jaundice and the hemorrhagic diathesis of the new born It is not indicated in the various hemophilic or menorrhagic purpura Hypoprothrombinemia and associated hemorrhage in the new born are effectively prevented by daily oral administration to the mother during her last few weeks in pregnancy To insure adequate protection for the infant vitamin K or its synthetic equivalent should be given promptly after birth and for several days thereafter Bleeding in hemorrhagic disease of the new born is controlled within eight hours

Clinical Observations on Effect of 3 3 Methylene bis 4 Hydroxycoumarin Louis P Wasserman and Daniel Stats (Mount Sinai Hosp New York City) gave

(5) A J M S p 466 4 Oct 1943

dicoumarin in repeated doses to 71 adults Of these 22 were selected only because they could remain in the hospital for two weeks and in the other 49 there was a definite indication for use of an anticoagulant

Oral administration of dicoumarin produces a marked fall (after a 24–72 hour latent period) in prothrombin content and prolongation of the coagulation time in most cases There is great variability in the degree of response and a definite fixed dosage schedule cannot be made Because of the variable response and latent period the drug has not always been useful in the therapy of arterial thrombosis or embolism arteriotomy or major pulmonary embolism Postoperative bleeding was observed in many cases when dicoumarin was given either before operation or shortly thereafter A tendency to hemorrhage was also noted in patients receiving dicoumarin in whom an unrelated lesion that might bleed was present e g bleeding into the skin in eczema bleeding from the kidneys in presence of renal calculus bleeding from leg ulcers in thrombo angiitis obliterans and bleeding into the pleural cavity following artificial pneumothorax Transfusions of fresh blood do not arrest the hemorrhagic tendency due to dicoumarin In several instances embolism thrombosis or progression of existing thrombosis occurred despite low prothrombin content induced by dicoumarin In 10 cases of occlusive peripheral vascular disease no symptomatic improvement was observed during a three month period while the prothrombin remained depressed as a result of dicoumarin It is possible that dicoumarin affects blood coagulation not only by lowering the prothrombin content but through other mechanisms Dicoumarin should not be administered if the prothrombin index is less than 50 per cent

Effect of Vitamin K_1 Oxide on Hypoprothrombinemia Induced by Dicumarol was studied in five patients by Charles S Davidson and Harriet MacDonald (Harvard

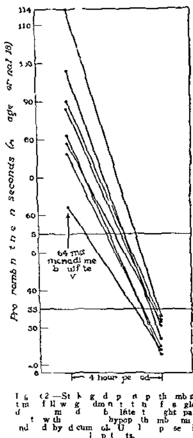
(*) New England J Med 9 353 355 Aug 6 1943

Univ) In one the preventive action of the vitamin was investigated Following administration of 500 mg dicumarol the prothrombin time rose from a normal value of 28 seconds to a maximum of 50 seconds two days later Twelve days later a second dose of 500 mg dicumarol was given followed in five hours by an intravenous injection of 180 mg vitamin K_1 oxide No significant change in prothrombin time occurred After 12 days dicumarol was given without vitamin K_1 oxide and the usual hypoprothrombinemia occurred In the other four patients vitamin K_1 oxide was given after hypoprothrombinemia from dicumarol had been established In two of these the prothrombin time returned to normal in 24 hours and in one in 14 hours The fourth patient did not respond presumably because the dose of the vitamin was too small The amount of vitamin K_1 oxide required to produce the desired effect varied from patient to patient no serious toxic manifestations were observed from administration of large amounts The only untoward effects observed were transient headache and in one patient vomiting

The effect of vitamin K_1 oxide presented here is confined to the action on hypoprothrombinemia produced by a single dose of dicumarol It will be necessary to establish the usefulness of the vitamin as a means of controlling the coagulation time in patients receiving a prolonged course of dicumarol If it is found that the vitamin acts similarly under these circumstances many of the dangers following the use of dicumarol can be averted

Effect of Large Doses of Menadione Bisulfite (Synthetic Vitamin K) on Excessive Hypoprothrombinemia Induced by Dicumarol Dicumarol has been used in a large number of cases during immediate postoperative periods for producing hypoprothrombinemia and thus preventing thrombophlebitis and pulmonary emboli However the danger of hemorrhage has prevented its general use Since experiments have indicated that large

doses of vitamin K have effect on hemorrhage following administration of dicumarol H E Cromer Jr and N W Barker determined to find out the effect of a single large do e of synthetic vitamin K on excessive hypoprothrombinemia induced by the usual do es of dicumarol



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The preparation used was dissolved in distilled water so that 1 cc solution contained 4 mg menadione bisulfite 62 5 per cent of which is menadione (synthetic vitamin K) All doses were given intravenously In the first seven cases the preparation of menadione bisulfite was diluted in 250–1 000 cc physiologic sodium chloride solution and given by the gravity method In the remaining 30 it was injected without dilution A single dose of 64 mg (16 cc of the solution) was given in almost all ca es No toxic or untoward reaction was observed

The 37 patients were hypersensitive to dicumarol a indicated by increase of prothrombin time to more than

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60 seconds after the usual doses of dicumarol had been given In 6 of the 37 cases excessive elevation of prothrombin time developed after administration of a single dose of 300 mg dicumarol in 6 immediately after administration of the first two doses of 300 and 200 mg on successive days in 11 on various days after the original two doses of 300 and 200 mg and in 14 at various period during treatment In the last 14 more than the original dose had been given

No response occurred in two cases In the other 3 the *prothrombin time fell to within safe limits* within 18 hours after intravenous injection of menadione bisulfite Rapid decrease of excessively elevated prothrombin *time following intravenous injection of 64 mg* menadione bisulfite was the usual type of striking response occurring in 81 1 per cent (Fig 62) In three cases there was *minimal lowering of prothrombin time* less than 15 seconds in 18 hours However even in these cases a definite inhibitory action was exerted confirmed by later administration of dicumarol

All patients were receiving dicumarol for a definite purpose and no attempt was made to return the *prothrombin time entirely to normal but merely to bring* it within therapeutically effective limits In absence of hemorrhage another dose usually 100 mg dicumarol was given *when prothrombin time fell to less than 35* seconds In three cases bleeding had occurred when the prothrombin time was excessively elevated it stopped within a few *hours after administration of menadione bisulfite* in two of these and after administration of menadione bisulfite and a single blood transfusion in one In a few cases in which tests for prothrombin time were done every two hours after administration of menadione bisulfite a definite lowering of prothrombin time was seen within 2 hours reaching a maximum in about 18 hours In almost all cases lowering of prothrombin time persisted until more dicumarol was given

DISEASES OF THE KIDNEYS

Glomerulonephritis Survey of Functional Organization of the Kidney in Various Stages of Diffuse Glomerulonephritis David P Earle Jr John V Taggart and James A Shannon (New York Univ) studied glomerular filtration rate (GF) renal plasma flow (PF) and maximal rate of tubular excretion of diodrast (Tm) in 22 patients with various phases of glomerulonephritis The glomerular filtration rate is the most sensitive indicator of renal change early in the course This is reflected by a low filtrate fraction and a low GF/Tm ratio There is a depression of all three functions as the disease advances associated with marked distortions in their normal relationships Acute glomerulonephritis and exacerbations in chronic glomerulonephritis may be associated with depression of glomerular filtration rate diodrast Tm filtrate fraction and GF/Tm ratio Any or all of these values may return toward normal as improvement or healing of the acute process occurs There may also be transient hyperemia indicated by a high PF/Tm ratio No correlation was found between changes in specific renal functions or their relationships in acute glomerulonephritis and the eventual outcome of the disease As chronic glomerulonephritis progresses tubular function undergoes relatively greater impairment than the glomerular filtration rate indicated by a high GF Tm ratio and a relatively excessive lowering of diodrast clearance The development of hypertension has not been specifically related to the residual kidney mass although it is not infrequent when there has been more than a 40 per cent reduction in Tm

It may be anticipated from these findings that the distortion of the normal quantitative relationship between glomerular and tubular function has important consequences to those mechanisms which are significant in determining the rate of excretion of water and electrolyte

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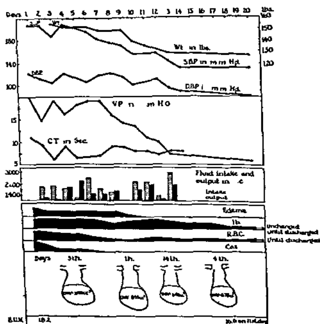
Glomerular damage out of proportion to impairment of tubular function should predispose to the retention of electrolyte and water as is so common The opposite combination however may contribute to demineralization which is seen frequently in later stages A low percentage of nephrons continuously diuretic because of impairment in electrolyte absorption can result in urine of low specific gravity This would explain the long persistence of impaired concentrating power noted frequently after healed acute diffuse glomerulonephritis

Role of Congestive Heart Failure in Production of Edema of Acute Glomerulonephritis John S LaDue (Louisiana State Univ) noted that most patients with congestive heart failure complicating acute glomerulonephritis also have peripheral edema therefore he attempted to correlate appearance and disappearance of edema with presence or removal of congestive heart failure He studied 12 patients with acute glomerulonephritis and peripheral edema Patients were put to bed and given no medication except magnesium sulfate to control convulsions Four patients were given low protein low salt diet four high protein low salt diet and four regular hospital diet There was no restriction of fluids but intake and output were charted Daily measurements of venous pressure circulation time blood pressure weight and degree of pulmonary hepatic or peripheral edema were recorded Teleroentgenograms and electrocardiograms were made frequently Urine was examined at least twice a week and blood urea and phenolsulfonphthalein excretion tests were done

The edema was found to be associated with right heart failure in every instance indicated by elevated venous pressure and cardiac dilatation In nine patients most of the symptoms of congestive heart failure were present but in three presence of peripheral edema was the only symptom suggesting heart failure More careful study of

(9) Ann Int Med 0 405 4 March 1944

the e three disclosed cardiac dilatation and elevated venous pre sure The importance of hypertension in pathogenesis and relief of the congestive heart failure which frequently complicates acute glomerulonephritis has been emphasized in the literature The earliest objective evidence of im provement of heart failure in seven of eight patients not



f 3 — gr 16 Fall bl od pr p ec ded fall ou p s- th d y dec ea f 155 d t l hea t l me w n ted f rt th d y d w 19 twenty f th d y 33

given digitalis was fall in blood pressure return to normal of the venous pressure and disappearance of edema oc curred slightly later The pulmonic second sound was accentuated in 11 patients suggesting the possibility of pulmonary hypertension in addition to proved systemic

hypertension in 4 patients whose heart failure disappeared before the blood pressure fell the pulmonic second sound remained markedly accentuated until fall in blood pressure occurred

Measurements of diastolic heart volume made within two weeks after compensation was established showed further decrease in diastolic heart volume of four patients This subsequent additional decrease in diastolic heart volume has also been noted in patients with congestive failure due to other causes Circulation time was normal or low in 11 patients despite elevation of venous pressure Elevation of venous pressure results in increase in capillary filtration pressure and thus probably was the mechanism of formation of the edema in the 12 patients In no instance were blood protein values decreased enough to account for the edema on the basis of diminution in osmotic pressure

***The Nephrotic Hypertensive Syndrome in Diabetes* and the Intercapillary Glomerulosclerosis of Kimmelstiel and Wilson** are discussed by Marc Aurot[1] *(Bern)* based *on four personal cases and review of the literature* Kimmelstiel and Wilson in 1936 described a peculiar primary hyalinization of the renal glomeruli which they designated intercapillary glomerulosclerosis The anatomic feature of the disease consists of hyaline masses which do *not* give the amyloid reaction in the center of the glomeruli or a capillary loop The adjacent capillaries are compressed so that the *endothelial nuclei come to lie in* onion peel formation in some areas the capillaries become dilated The afferent arterioles may also be hyalinized The thickened glomerular capsule occasionally contain lipoid deposits These pathologic findings correspond to a well defined clinical syndrome of diabetes with albuminuria hypertension and nephrotic type of edema *The disease* occurs almost exclusively in persons over 40 and is more common in women than in men Over 35 case

(1) S hw m d Wel sch 7 2 9 995 A g 14 1943

have been reported in the literature in most of which clinical and anatomic data were pre ented Whereas Kimmelstiel and Wilson see only a quantitative differ ence between intercapillary glomerulosclerosis and nephro sclerosis Allen using special stains finds distinct patho logic differences between the two conditions and maintains that in intercapillary glomerulo clerosis the hyaline masses lie not in the intercapillary connective tissue but in the capillary wall itself notably in the subendothelial basal membrane

Diabetes usually mild and not requiring insulin treat ment is found in most cases Since the renal component of the syndrome may cause a rise in the threshold of sugar excretion there may be a discrepancy between urine and blood sugar values Glycosuria may at times disappear Therefore an elderly patient pre enting a nephrotic hy perten ive syndrome should always be examined for masked diabete Albuminuria may reach high proportions and i rarely present in trace only The sediment may sh w besides erythrocytes and asts double refracting elements Depending on the extent of the glomerular sclerosis all ta es of renal insufficiency to uremia may be represented Hyperten ion is a cardinal symptom but may be missing Severe sclerotic changes in the ocular fundi occasionally accompanied by hemorrhages and exudation are a con tant finding The nephrotic syndrome includes gener il i ed edema and hypoproteinemia with reverse albumin globulin ratio and hypercholesteremia is frequently but not invariably present Associated symptoms may be cardiac changes neuriti ot the lower extremities and hypochromic anemia

A hi tory of acute glomerulonephritis may aid in differ entiating the disease from chronic glomerulonephritis with a nephrotic component occurring in diabetics and of a primary cardiac disease from the diabetic nephrotic hyper tensive yndrome occurring in the late cachectic stage of cardiac insufficiency Lipoid nephrosis occurs in young

hypertension in 4 patients whose heart failure disappeared before the blood pressure fell the pulmonic second sound remained markedly accentuated until fall in blood pressure occurred

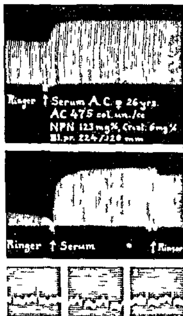
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(1) Schw z m d Wchn h 3 989-993 A g 14 1943

and heart muscle of uremic patients Correlations were made with the electrocardiogram and clinical picture and comparative experiments with uremic serum and with various catechols and phenols were done on the isolated frog heart and on the intact rabbit

Excessive accumulation of catechol compounds (AC) of probably adrenosympathetic origin (adrenalin and related substances) *in the blood* as well as heart muscles was a characteristic feature of uremia in 28 cases With few exceptions the patients displayed signs of cardiac failure and marked abnormalities of the electrocardiogram of the anoxic type The uremic serums examined showed specific intensely cardiotoxic properties as manifested by their effects on the isolated frog heart (Fig 64) and on the rabbit's electrocardiogram The latter effects were produced by protein free serum extracts which contained the entire



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catechol material and which proved rapidly fatal Correlation of clinical biochemical and experimental findings suggested the probable identity of the excess catechol material present in the uremic blood and myocardium with at least part of the cardiotoxic substances present in the uremic serum To substantiate this concept model experi

individuals and there are no hypertension and ocular changes in amyloid nephrosis there are known etiology amyloidosis in other organs and a positive congo red reaction Anatomically differentiation from intracapillary glomerulonephritis with hyalinization when there are no inflammatory signs or fusion of the capillary loops with the capsule is almost impossible except for the different picture of the basal capillary membrane

Since intercapillary glomerulosclerosis rarely occurs in nondiabetics diabetes and advanced age may be assumed to be the etiologic factors of the disease

Interrelations of Serum Lipids in Patients with Diseases of Kidney John P Peters and Evelyn B Man (Yale Univ) analyzed the lipids of the serum of patients with kidney diseases

Cholesterol was frequently elevated in the serum of patients with renal disease characterized by edema associated with hypoproteinemia whether they had a true nephrotic syndrome or not The hypercholesteremia could not be correlated with any single feature of these diseases The partition of cholesterol was not regularly distorted The relation of cholesterol to lipid phosphorus usually was not disturbed following the same course described for normal persons and patients with thyroid disease Both cholesterol and lipid phosphorus fell when the renal disease cleared or when renal failure developed They may also fall during exacerbations or other complications that interfere with feeding and impair nutrition Neutral fat was usually distinctly elevated when hypercholesteremia was present In patients with arterial disease and hypertension without evidence of antecedent renal disease the concentrations and proportions of cholesterol lipid phosphorus and neutral fat were normal

Cardiotoxic Substances in Blood and Heart Muscle in Uremia. W Raab[3] (Univ of Vermont) studied the behavior of adsorbable chromogens (AC) found in the blood

( ) J Clin. Investigation 2 7 1 726 September 1943
(3) J Lab & Clin. Med. 9 715 34 July 1944

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Fg 5—T b l dg t T l l ra t d f m h th ty d m to t tt l ts M y t b l , h l l ll h l t t t *th b m m mb d g l ll g l d cu l t d* N l bs t m ll d p k t h ln m t t b l p h l m c d d to hyp h m t f ll h g pr nc f g t ll H m t yl o

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There is no indication from the chemical findings that *adrenalin proper forms a major fraction of the excess* catechol compounds accumulated in the uremic organism however altered adrenalin and other adrenalin like substances produced by the adrenal medulla and possibly by the entire sympathetic nervous system probably are *retained* in the body in conditions of advanced renal excretory insufficiency The general toxic effects of catechol compounds on the heart muscle are most strikingly exemplified by adrenalin—stimulation as well as inhibition myocardial anoxia structural damage and failure but since the catechol nucleus is believed to be essentially responsible for the pharmacodynamic effects of adrenalin and for its high electric potential it appears reasonable to ascribe adrenalin like cardiotoxic effects also to other biologic catechol compounds as found in excess in the uremic organisms

Besides catechols intestinal phenols also form part of the abnormal material which accumulates in the uremic blood and they too possess certain cardiotoxic properties (bradycardia decrease of amplitude) and therefore *must* be considered as participating in the chemical mechanisms which produce cardiac damage and ultimately cardiac death in many uremic patients

Clinicopathologic Studies of Renal Damage Due to Sulfonamide Compounds Francis D Murphy Joseph F Kuzma Theodore Z Polley and John Grill (Marquette

(4 A h I t Med 3 433 443 J 1944

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F g 6 —T bul d gen t T l l p ed f m e h othe t d ma t t ual t e. M y t b l p h l l lls h lo t t ct b n t m mb n and g l ll g l l l l l) bse t some c ls d pyknot h l som tance t bul p th l m cond sed to hype h omat ma f ll b ng ppea nc t g t ll ll mat yl o n.

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(4) A h Int Med 73 433 443 Ju e 1944

degeneration with necrosis of the pyramids and the third is typical of extensive glomerular involvement with wide spread tubular injury

Acute Porphyria Samuel Nesbitt (Yale Univ) re views the clinical aspects of the condition and reports three cases The porphyrias are classified as congenital acute and chronic Congenital porphyria appears early in life or at birth and is characterized by excretion of large amounts of porphyrin particularly uroporphyrin I in the urine so that it may be dark red at times photosensitivity pre dominance in males and discoloration of the teeth by im pregnated uroporphyrin It is an extremely chronic disease the outstanding features of which are blistering scar forma tion and eventual deformity of the exposed parts as a result of light sensitivity

Acute porphyria is classified on the basis of the clinical picture as the classic type with abdominal and nervous manifestations the abdominal type with abdominal colic only the purely nervous type with central nervous system manifestations without abdominal colic the comatose type in which severe central nervous system involvement with coma is outstanding and the latent type which is asymp tomatic despite laboratory evidence of fundamental pig ment disorder However since *these are descriptive terms* a case may belong to any one of the various types The disease may be of long standing with ill defined symptoms including vague poorly localized abdominal pain bizarre pains in the extremities or elsewhere nervousness in somnia depression and generalized or localized weakness the urine occasionally may be dark red or unusually dark The acute episode is characterized chiefly by gastro in testinal disturbances and involvement of the central nervous system There are usually associated nausea vomiting and constipation there may or may not be fever or leukocytosis Roentgen examination may reveal dilatation of some seg ment of the gastro-intestinal tract usually the duodenum

( ) J A M A 1 4 8 94 J 9 1944

The authors observed 14 patients in whom renal damage developed after sulfonamide therapy for various conditions sulfathiazole in 7 sulfadiazine with sulfathiazole in 1 sulfadiazine alone in 2 sulfanilamide in 3 and sulfacetimide with sulfathiazole in 1 Dosage consisted of 2-3 Gm initially and 1 Gm thereafter every four hours until discontinuance Large t tot d do e in any case was 41 Gm and the smallest 0 6 Gm average dose before renal dama e appeared being 20 Gm Five patients had mild albuminuria without other evidence of renal involvement before the drug was given but no correlation could be found between presence of albumin in the urine and the peed with which subsequent oliguria and anuria developed Avera e time for development of signs of renal damage was four days Oliguria was the first evidence of severe renal insufficiency in 12 cases anuria in 1 and generalized edema in 1 In five cases red blood cell casts albumin and sulfonamide crystals were associated with oliguria In seven ca e ct oliguria red cells casts and albumin were present but crystals were absent In all but four cases there was retention of nitrogenous substances in the blood No correlation was found between the height of blood level of sulfonamide and the type of renal damage

Five patients died of uremia due to intoxication with the sulfonamide and one of uremia due to nephritis One died of streptococcic septicemia another of septicemia secondary to septic endometritis and one of sepsis with generalized peritonitis Lobar pneumonia in one case complicated by pulmonary ab cess accounted for two deaths and bronchopneumonia for one One patient died of portal cirrhosis associated with heart disease The last patient ur vived after decapsulation of the kidney

Three cases are reported in detail to illustrate the types of renal damage the first case exemplifies the simple type of damage to the kidney due to toxic effects of sulfonamide associated with ob truction (Fig 65) the second ca e represents the group characterized by extensive tubular

quency The series included nine males and seven females Six of the nine patients who lived more than one month died of hypertension each with extensive disease of the functioning kidney Four three females and one male had developmental defects of the genital tract

Renal aplasia can seldom be differentiated clinically from renal agenesia Surgical exploration for and removal of an aplastic kidney are indicated for relief of pain in patients with intractable hypertension and no evidence of disease of the functioning kidney and in patients with hypertension when pyelonephritic contracture or renal hypoplasia cannot be excluded

Congenital Renal Hypoplasia Associated with Hypertension Daniel R Higbee (Denver) reports two cases of renal hypoplasia defined as miniature or rudimentary kidney

CASE 1—Girl 12 overweight had had pyelitis six years before with mild subsequent recurrences family history revealed hypertension in the mother Blood pressure was 180 110 Urologic examination showed a small well formed infantile kidney on the right and a greatly hypertrophied kidney on the left Appearance time was normal on the left and 12 minutes on the right with poor dye concentration and a volume of urine about one fifth that on the left Blood pressure for several weeks ranged between 160 and 170 over 110 Following nephrectomy it gradually fell to 110 and 120 over 80 which has been maintained for 13 months The kidney weighed 21 Gm and measured 6 × 3 5 × 1 5 cm It was either a normal kidney atrophied by chronic infection or a congenitally hypoplastic one with superimposed sclerosis The smooth outline and regular well formed collecting system seemed to indicate that it was primarily hypoplastic with superimposed sclerotic changes Microscopic examination showed areas of normal kidney tissue adjoining areas in which marked sclerosis and arterial changes had taken place typical of the type of lesion most commonly found responsible for hypertension Considering the patient s age the probably short period of elevated pressure and the favorable postoperative response in pressure the improvement may be permanent

CASE 2—Woman 45 had pain in the left lumbar region

terminal ileum or a segment of the colon Central nervous system involvement may be manifested by symptoms ranging from paresthesias and pain in the extremities to paralysis delirium with hallucinations of vision and hearing epileptic seizures and coma Diagnosis of acute porphyria depends on evaluation of the clinical picture and examination of the urine as confirmation Almost all patients with acute porphyria excrete uroporphyrins III and I in the urine with predominance of the type III isomer

Three cases of acute porphyria occurring in the same family indicated that the disease is as much familial as congenital and that the underlying mechanism is an inborn error of pigment metabolism as suggested by Gunther Case 1 represents the picture of classic acute porphyria with a changing neurologic picture Autopsy findings were disappointing The zinc content of liver and pancreas was not abnormal and would indicate that zinc depletion is not a factor of the disease even though the disease is characterized by the excretion of the zinc metal complex of uroporphyrin Case 2 is unusual because of the predominance of the isomeric series I of uroporphyrin and coproporphyrin in the excreted urine Cases 2 and 3 are examples of latent porphyria in which there are no clinical manifestations

Renal Aplasia Earl E Nation reports 16 cases found in 27 000 autopsies at Los Angeles County General Hospital He defines renal aplasia as incomplete or defectively developed kidneys as distinguished from renal agenesia in which no vestige of renal tissue is found To distinguish it from hypoplasia and secondary atrophy renal aplasia is properly used only to denote presence of tissue of metanephric origin which has never developed any renal function or has undergone congenital atrophy It usually results from failure of proper contact between the ureter and the metanephros Of the 16 cases 3 were bilateral The right and left kidneys were involved with equal fre

(6) J Urol 51 579 580 J 1944

retains any function is likely to increase severity of the hypertension rather than improve it even though function of the opposite kidney is normal Usual tests of renal function may be unreliable therefore special care must be

PATHOLOGIC CONDITIONS IN REMOVED KIDNEYS

Type of Renal Disease	B/P Unchanged	B/P Reduced: Normal	B/P Reduced: To Normal Lowered Less Than 2 Yr	B/P Normal After 2 Yr or More
Chronic pyelonephritis	21	13	13	1
Renal tuberculosis	1	[illegible]	—	2
Renal calculi and pyelonephritis	1	4	1	—
Aberrant renal artery with hydronephrosis			—	1*
Renal infarction			1	
Occlusion of renal artery		—	—	1
Traumatic renal injuries		1	1	—
Hypoplastic kidneys		—	1	
Hypernephroma	5	2	1	—
Wilms's tumor			1	
Total	8	[illegible]	19	5

I d q ate p e pe t blood p s d g

given to evaluation of function of each kidney before nephrectomy is done

Thrombosis of Renal Vein William F Melick and Alvin E Vitt (St Louis Univ) state that in children renal vein thrombosis usually occurs after ileocolitis In adults thrombosis is usually due to perirenal suppurations renal abscesses or pyelonephritis it may also be secondary to ascending venous thrombosis originating in veins of the pelvis or lower extremities or to renal tumor Until last year the diagnosis had never been made preoperatively Campbell and Matthews obtained a retrograde pyelogram

(9) J L 1 51 587 596 J 1944

with repeated attacks of cystitis and recently discovered hypertension she had had three previous abdominal operations Urologic examination showed a small *peculiarly formed* left kidney and a somewhat larger than average right kidney associated with congenital enlargement of the upper major calyx Tests were normal on the right side Urinary volume while excellent from the right kidney was practically nil from the left as were the dye tests During two months blood pressure ranged from 180 to 160 over 110 to 100 Nephrectomy was advised primarily for relief of pain and infection Blood pressure readings during hospitalization and *thereafter showed a gradual fall in pressure to systolic 120–*140 with diastolic 90–95 After eight months of observation pain and infection had not returned and blood pressure had not increased The gross specimen was a small fibrotic kidney 1 4 × 2 0 × 2 7 cm with an adherent capsule Microscopic changes in the kidney were not as typical as those in Case 1 sclerosis was more generalized and extensive In view of these factors and the patient s age there may be eventual return of elevated blood pressure in that instance the im*provement has been merely coincidental*

Effects of Unilateral Nephrectomy in Treatment of Hypertension Willis Sensenbach (Wake Forest College) reports 4 cases and reviews 75 in the literature Only five cases (see Table) meet the requirements for cure after nephrectomy In about one third blood pressure fell to normal but the patients had been followed less than two years One third had reduction in blood pressure but remained hypertensive while in one third blood pressure was unchanged or increased

The following criteria for selection of patients with hypertension for nephrectomy should be rigidly met if reasonable success is to be attained (1) The diseased kidney must be functionless or nearly so (2) The opposite kidney must function normally (3) Hypertension should be of short duration Other factors being equal the younger the patient the greater the chances of favorable results A two year follow up is necessary before hypertension can be considered cured by nephrectomy Removal of a kidney if it

(8) A h I t M d 73 5 3 130 F b ry 1944

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(8) Arch. Int. Med. 73:123-130, February, 1944.

proteins 6.05 Gm albumin 3.37 Gm globulin 2.68 Gm prothrombin time 36 seconds (normal 32 seconds) Blood culture was positive for hemolytic taphylococcus Chest film showed infiltration in the lower lobe of the left lung Administration of sulfathiazole and sulfadiazine transfusion bed rest and elevation and immobilization of the left leg brought improvement White cell and differential counts became normal and blood cultures negative for two days

Then the temperature rose again there was a severe chill the white cell count rose and showed marked shift to the left and he complained of severe right loin pain There was marked costovertebral angle tenderness on the right and the right kidney was enlarged and exquisitely tender while the left kidney appeared normal White cell count was 18,500 with marked shift to the left Urine was normal Prothrombin time was 57 seconds hematocrit reading 19 and sedimentation rate 0.36 A flat plate of the abdomen showed an enlarged right kidney and absence of the right psoas muscle shadow Transfusion was given Cystoscopy showed no urine coming from the right ureteral orifice gentle lavage with sterile water returned *old blood and small clots from the pelvis* *Intravenous* phthalein appeared on the left in 3 minutes and reached good concentration in 5 but there was no trace on the right after 30 minutes Culture was negative Retrograde instillation of opaque medium produced a bizarre pyelogram The right renal pelvis was poorly visualized irregularly filled and irregular in outline the left was normal A lateral pyelogram showed no displacement of the right kidney but poor filling of the renal pelvis

Exposure of the right kidney showed it three times normal size a deep purple black with discrete pale yellow patches Palpation of the pedicle showed the renal vein thrombosed The kidney was removed Convalescence was fair with slowly falling temperature and return to normal of blood counts Thrombophlebitis in the right leg was improved with ice packs and pillow splints Prothrombin time was 47 seconds (normal 45)

Examination of the right kidney showed the large veins completely occluded by fresh thrombotic material in which leukocytes were prominent (Fig 66) Venous walls and adjacent surrounding tissues showed considerable inflammatory reaction and were extensively infiltrated by neutrophilic leukocytes Adjacent arterial wall was uninvolved and the arterial lumen was free from thrombus The phlebothrombotic process also involved the smaller vein of the medulla The parenchy

by forcing the medium into a blocked off pelvis thus producing marked infiltration into the renal tissues

The authors report a case in which a retrograde pyelogram was secured which showed the early roentgenologic changes of renal vein thrombosis

Woman 33 complained of chill fever shortness of breath pain in the right chest and back and swelling of the left leg



Fig 66—La g e f h l Wall f n filt t d by le kocyt s th b oc l d t l m n

for a week After delivery of a normal child one month previously she had had a normal postpartum course She appeared anemic and in severe pain The leg was swollen and edematous with pitting edema most marked around the ankle A catheterized urine specimen showed specific gravity 1 030 pH 6 no albumin or sugar an occasional red and white cell but no bacteria Blood showed white cell count 17 750 with marked shift to the left red cell count 2 870 000 hemoglobin 9 5 Gm nonprotein nitrogen 32 sugar 101 diastase 38 units icteric index 6 van den Bergh reaction negative plasma

bosis Tumor thrombosis was found in 49 8 per cent of hypernephromas grades 1 and 2 and in 61 9 per cent of those grades 3 and 4 Presence of tumor thrombosis increases the gravity of prognosis regardless of the grade of malignancy

In 76 cases the tumor was classified as carcinoma of the renal pelvis Involvement of the perineural lymphatics in the hilus of the kidney or tumor thrombosis of the renal vein was present in 34 Only 1 of the 34 patients survived five years after dismissal

Tumor thrombosis of the renal vein or involvement of the perineural lymphatics or both were present in 14 of 31 cases of Wilms s tumor neither had material influence on the five year survival rate in this group



F g 67 —Sect n f ma n nal d l art y A te y h d f th mbosis n, h w er fill d w h mal gn t th mbu ec d y t hypern ph m f k d y H mato yl eo n × 39

Tumor thrombosis was present in the renal vein in 2 of the 20 cases of sarcoma of the kidney No instance of involvement of perineural lymphatics was encountered and presence of tumor thrombus had no prognostic significance

Wilms s Tumor of the Kidney Clinicopathologic Study of 44 Proved Cases Wilson Weisel Malcolm B Dockerty and James T Priestley state that Wilms s tumor though the commonest malignant abdominal tumor of children occurs once among 25 000 patients coming to the Mayo Clinic Twenty nine of the 44 patients were females Ages ranged from 7 months to 59 years the greatest number of

( ) J U 50 399 413 October 1943

matous tissue was extensively involved by widespread degeneration and necrotic lesions In the patchy areas of most severe involvement coagulative necrosis or infarction was present with loss of nuclei of glomerular and tubular cells diffuse eosin staining and extensive infiltration by neutrophilic leukocytes In less affected areas there were necrosis and desquamation of tubular lining cells but glomerular tufts appeared still viable Even in the least damaged areas there were severe degeneration of tubular lining cells and marked edema of interstitial tissues The medulla was damaged and large areas completely necrotic

Malignant Tumors of the Kidney Surgical and Prognostic Significance of Tumor Thrombosis of the Renal Vein is discussed by *John R McDonald* and *James T Priestley* (Mayo Clinic) on the basis of a study of 636 kidneys containing malignant neoplasms The recognition of a tumor thrombus in the renal vein is of surgical and prognostic importance At the time of operation the surgeon always adheres to certain principles in mobilization of the growth because of the possible existence of a tumor thrombus If a tumor thrombus is found early in the operation certain special procedures must be used to reduce the risk of operation

In 509 cases the tumor was classified as hypernephroma (carcinoma of renal cortex) In 275 of these malignant thrombosis of the renal vein was present Involvement of perineural lymphatics was observed in one The arterial tree was not invaded probably because of the greater resistance of the walls of arterioles The thrombosis may extend a varying distance along the renal vein and may even involve the vena cava The thrombus becomes firmly attached to the intima of the vein as it grows a point of importance in regard to removal of the thrombus Mortality rate during the first year following operation for hypernephroma was 38 per cent among patients with tumor thrombosis and 18 per cent among those without thrombosis The five year survival rate was 55 4 per cent among patients without and 29 per cent among those with throm

(1) S rg Gynec & Ob t 7 9 336 S pt mbe 1943

DISEASES *of the* HEART *and* BLOOD VESSELS

WILLIAM D STROUD M D

cases occurring in the third year 31 patients were under 6 and only 7 over 12 Lump in abdomen and swelling of abdomen were the commonest complaint Hematuria was the cardinal symptom in five cases and was apparently considered of secondary importance in nine other Pain was the presenting symptom in three and a minor symptom in five It was usually dull but in several instances colicky related to passage of blood clots down the ureter Fever was present in half the cases and emaciation and cachexia in one third Symptoms were generally progressive with average duration of 4½ month Presence of an abdominal mass was the most important single diagnostic sign Ascites was present in several cases Secondary anemia was noted in most and mild leukocytosis in 15 Albuminuria was found in 19 and microscopic evidence of hematuria in 11 Roentgen diagnosis was made in 15 cases The retrograde urogram is most useful in differentiation

Nephrectomy was *performed in 42 cases and* exploratory operation in 2 Only seven patients were living 2-20 year after operation Of those who died only six survived the operation for one to four years At present the treatment of choice is considered to be immediate nephrectomy combined in cases of larger tumors with preoperative irradiation and always postoperative roentgen treatment

All tumors were unilateral Size varied from 30 × 15 × 12 cm to 4 × 3 × 2 5 cm Nearly all showed degree of encapsulation *33* were nodular or lobulated the remainder globoid or unicentric Thirty three showed cystic usually hemorrhagic centers Diagnosis was based on the combination of carcinoma like cells in tubular cylindroid papillary and *solid arrangement and spindle shaped sarcomatous* cell Striated muscle cells probably representing variants of the ordinary stromal elements of the tumor were found in 45 5 per cent Roentgen therapy usually induced widespread necrosis of tumor cells but viable nests of highly malignant cells were always found showing that a long interval between irradiation and operation is unwise

PART IV

DISEASES OF THE HEART AND BLOOD VESSELS

INTRODUCTION

In this series as during the past 14 years the articles will be found grouped under the headings as outlined in the nomenclature and criteria for diagnosis of diseases of the heart revised by the Criteria Committee of the New York Heart Association (Arthur C DeGraff M D Clarence E de la Chapelle M D Carey Eggleston M D Charles E Kossmann M D Robert L Levy M D John B Schwedel M D and Harold F B Pardee M D chairman) This nomenclature and criteria for diagnosis have been approved by the American Heart Association and copies may be obtained through its main office at 1790 Broadway New York City

—WILLIAM D STROUD

ETIOLOGIC DIAGNOSIS

ARTERIOSCLEROSIS

Alcohol and Iodine in Relation to Arteriosclerosis According to Djamil Faik Tutunji (Amman Transjordan) alcohol in moderate doses is beneficial in arteriosclerosis and iodine is harmful in the nonsyphilitic cases This opinion is based on the theory that hypercholesteremia is the cause of arteriosclerosis If this is true an ideal preventive and possibly curative drug should be a solvent of cholesterol to prevent its deposition in the arterial walls it should also be a vasodilator Alcohol fulfils these requirements with the additional advantage that it is also oxidized in the body without leaving any residue to overburden the excretory organs and thus makes up for quantitative limitation of diet by supplying about 100–300 calories

Tutunji recommends use of alcohol in arteriosclerosis in the form of whisky or brandy in daily doses of 30–90 cc.

(1) Acta med. orient 58 60 M h 1943

clude clearcut evidence of organic valvular disease or of congenital anomaly, clinical phenomena of infection, i.e., fever, leukocytosis and increased sedimentation rate, embolic manifestations, and repeated isolation of Streptococcus viridans by blood culture. Cary Eggleston (Cornell Univ.) stresses that accuracy of diagnosis is essential to correct interpretation of results of treatment. Subacute bacterial endocarditis is subject to spontaneous remissions for weeks or even months which may simulate cure. Hence observations must be extended sufficiently long to exclude this possibility.

To be effective in this disease, any chemotherapeutic agent should be present in active form and in considerable concentration in the blood plasma. Its toxicity to the streptococcus *should be greater than that to the host or his* tissues. The drug should not leave the blood stream too rapidly; its antibacterial properties should not be neutralized by blood or tissues of the host and it should be able to penetrate the fibrin and blood clot which surround the foci of living, multiplying organisms in concentrations adequate at least to be inhibitory. Advent of sulfonamides gave rise to renewed hope. Compared with mercury or arsenical compounds which have been used and found wanting, the sulfonamides are relatively harmless; they are highly bacteriostatic for Streptococcus viridans in concentrations in the blood which can be secured and maintained readily and are powerfully inhibitory to growth of all streptococci. In subacute bacterial endocarditis the *bactericidal titer of the blood usually is high and is not* impaired by sulfonamides.

Most if not all of the absorbable sulfonamides have been used in attempted treatment of subacute bacterial endocarditis. In a recent review of reported results, Lichtman collected 2,596 cases in which spontaneous recovery was noted in 1 per cent. Under treatment with sulfonamide alone 21 of 459 patients recovered, a rate of 4 per cent. Sixteen of the recoveries occurred in patients infected

[illegible] M. I. C. ... f C. ... D. ... 33 J. ... 1944

He suggests that alcohol may be used intravenously (since this has been found practicable in treatment of tetanus) during anginal attacks and in patients with excessive arterial tension. When religious prejudice against alcohol makes its use impossible, sclerolysin, a colloidal phosphatide that is a cholesterol solvent, is recommended.

The harmful effect of iodine in nonsyphilitic arteriosclerosis is probably due to its stimulating effect on the thyroid.

Vertigo and Related Conditions. Maurice Eliaser Jr (M.C., U.S.A.) suggests that vertigo, giddiness, light headedness and syncope are manifestations of cerebral anoxemia resulting from cerebral arteriosclerosis. Because of effects of gravity involved in venous return from the brain, there may be disparity between cerebral volume blood inflow and outflow when arterial circulation is impaired. This cannot be appreciably improved by attempted improvement of arterial circulation, but venous circulation of the intracranial contents is amenable to change since the entire venous return is ultimately carried by the jugular veins. With the object of obstructing venous return, an elastic collar 3/8 in. wide was devised; it is adjustable and may be tightened sufficiently to cause engorgement of jugular vein without impairing arterial circulation. Patients were advised to put it on 15 minutes before arising in the morning and to wear it continuously until night, when it was to be removed 15 minutes after retiring. This produced marked improvement in subjective symptoms in patients with cerebral arteriosclerosis. Theoretically, use of the collar seems indicated in other conditions, e.g., cerebral arterial thrombosis during its early phase, postural hypotension if unassociated with intrinsic arterial disease, and for amelioration of symptoms noted by pilots during rapid descent.

BACTERIAL INFECTION

Chemotherapy in Subacute Bacterial Endocarditis. Essential requirements for diagnosis of this condition in

(1) J. L. & Cl. M. [illegible] July 1944

units per cc penicillin Daily dosage varied from 40 000 to 200 000 Florey units and total from 867 920 to 7 890 340 Florey units Heparin dosage approximated 300 mg every second day when given subcutaneously and 200 mg daily when incorporated in veno lysis Heparinization was checked by the Lee White modification of Howell s method for determining coagulation time A reading of 50-60 minutes was regarded as satisfactory evidence of anti coagulant activity

Immediate effects of treatment suggest uniformly successful sterilization of blood and relief of clinical manifestations Penicillin was administered by continuous intravenous drip one patient also received the drug intramuscularly Heparin was given subcutaneously in most instances but was occasionally given in the intravenous infusion

Treatment produced no evidence of toxicity and all the patients exhibited striking well being during and after the active period of treatment In a few patients efficacy of the therapy may have been enhanced by preliminary use of sulfonamide Post therapy management included removal of possible foci in teeth and nasopharynx with prophylactic chemotherapy with penicillin

[It is most heartening to read of many apparently authenticated cures of this dread disease by the use of penicillin with or without heparin —Ed]

Myocarditis in Children was observed 97 times in 1 420 autopsies on patients *8 days to 16 years old* by *Otto Saphir* Simon A Wile and Irving M Reingold (Michael Reese Hosp) Incidence in 3 712 autopsies on adults during the same period was 4 05 per cent Postdiphtheric inflammation of the myocardium was diagnosed in 1 of the 97 cases Myocarditis was associated with meningitis in 4 cases poliomyelitis in 7 bronchopneumonia in 12 lobar pneumonia in 3 and nephritis in 3 There were 16 cases of myocardial abscesses 5 of myocarditis associated with bacterial endocarditis 7 of myocarditis associated with subacute bacterial endocarditis 13 of a rheumatic type

(5) Am J D Child 67 94 112 Apr 1944

with Streptococcus viridans When heparin was given with sulfonamide there were 6 5 per cent recoveries in 109 patients The same recovery rate followed combination of sulfonamide with physically induced fever in 61 patients Sulfonamide treatment combined with intravenous typhoid vaccine cured 7 of 45 patients so treated (15 5 per cent)

Chemotherapy alone or combined seems definitely to have raised the rate of recovery significantly above that of spontaneous cure Sulfonamides combined with heparin or artificial fever have probably saved numerous lives and this represents the first real advance in treatment of this well nigh uniformly fatal infection Still chemotherapy of subacute bacterial endocarditis remains clearly rather dis appointing Failure to obtain a higher measure of success seems to be largely inherent in the disease itself and to a lesser degree in such potentially controllable factors as determination of susceptibility of the infecting strain of organism and avoidance of artificial production of acquired resistance to the chemotherapeutic agent It has been shown experimentally that although sulfonamides may be present in high concentration they do not penetrate the surround ing fibrin and blood clot which mechanically isolate the nidus of living organisms Perhaps some new derivative may yet be developed with greater powers of penetration Value of penicillin in subacute bacterial endocarditis is yet to be determined

Combined Penicillin and Heparin Therapy of Subacute Bacterial Endocarditis Leo Loewe Philip Rosenblatt Harry J Greene and Mortimer Russell (Jewish Hosp Brooklyn) report apparently successful treatment of seven consecutive cases Six patients had bacterial endocarditis engrafted on chronic rheumatic valvulitis the seventh had a congenital cardiac defect In five the etiologic organism was Streptococcus viridans one had a hemolytic strepto coccus and the other a pneumococcus type XXVII

Probatory sensitivity tests were performed bacteria were inhibited within the dilution of 0 007-0 01 Florey

(4) J A M A 124 144 149 Ja 15 1944

no evidence of cardiac disability Young men with this lesion have worked at hard labor with no symptom of cardiac strain Women have borne children with no signs of heart failure Such observation lead to an attitude of conservatism

Six illustrative ca e are cited Three indicate no need for urgery since two patient were in excellent health de pite definite evidence of patent ductus arterio u The



Fig 68 T l en g m f h rt

other patient a man 58 who had done manual labor all his life died as a result of noncardiac complications following total gastrectomy for stomach carcinoma Teleroentgenogram of the heart (Fig 68) and postmortem examination (Fig 69) revealed an enlarged heart and open ductu arteriosus The other three ca es illustrate the other ide of the picture that good adjustment and freedom from cardiac di ability is no guarantee that subacute bacterial endarteritis may not intervene at any time or that cardiac

of myocarditis 19 of rheumatic myocarditis 3 of isolated myocarditis and 4 of myocarditis with tuberculosis

Clinically myocarditis may be suspected if during the course of an infectious disease a child suddenly becomes worse and begins to fail without apparent cause Tachycardia out of proportion to temperature particularly if accompanied by cyanosis is an early sign that may direct attention to the myocardium Cardiac enlargement is frequently present and blood pressure usually is low The electrocardiogram sometimes reveals significant changes Evidence of heart failure was noted 32 times in this series of cases In most patients a diagnosis of rheumatic heart disease was made Sudden death occurred in 9 of 60 children whose clinical records were available

It is evident that myocardial damage in children may and does occur in diseases other than rheumatic fever and diphtheria Inflammatory myocardial damage occurs in scarlet fever meningitis and poliomyelitis but is rarely encountered in measles mumps whooping cough smallpox or varicella Myocarditis is often encountered and rarely diagnosed clinically in bacterial and subacute bacterial endocarditis The only type recognized and diagnosed clinically with any degree of frequency is that occurring with rheumatic endocarditis and the rheumatic type of endocarditis

CONGENITAL ANOMALY

Prognosis of Untreated Patent Ductus Arteriosus and Results of Surgical Intervention M J Shapiro and Ancel Keys (Univ of Minnesota) discuss a clinical series of 51 cases and analyze 140 operations (representing data on nearly all patients on whom ligation of the ductus has been attempted) This study was undertaken to determine if possible the need for surgery in these cases During years of observation the authors were impressed with the apparent innocuousness of this lesion Children observed through their entire school careers were able to carry on regular school activities with no restrictions and showed

(65) Am J M Sc 206 1 4 383 Sept 1943

most of the remainder died of congestive heart failure Spontaneous rupture of the pulmonary artery or the ductus occurred *in a few instances The average age of the* authors entire series of 51 patients is less than 25 years and the oldest patient died at 58 It is true that most of these patients were found in a children s clinic but the authors made considerable efforts to find adult cases with no great success These data force reconsideration of a con servative attitude toward what might seem radical surgery

RESULTS OF SURGERY ON PATIENT WITH PATENT DUCTUS ARTERIOSUS

Total number surgeons	25
Total patients operated on	140
Uninfected patients	107
1 Completely successful result	81
2 Persistence of continuous murmur	14
3 Rupture of duct at operation	6
4 Operation followed by subacut bacterial endarteritis	2
5 Infection of wound and mediastin tis	1
6 Condition found inoperable	1
7 Vessel ligated not ductu arterio us	3
8 Error in diagnosis	2
9 Total number dead after operation	9
Patients operated on with subacute bacterial endarteritis	33
1 Completely successful results	20
2 Died at operation	5
3 Fever persi ts after succes ful l gati	8

The surgical data accumulated by Shapiro and Keys are shown in the table They conclude that surgery is advis able for most patients with patent ductus arteriosus with or without subacute bacterial endarteritis Experience of Touroff and others operating in the presence of subacute infection shows that ligation should be attempted imme diately once the diagnosis is made Continued presence of infection renders operation much more hazardous because of increasing edema and friability of the ductus and adja cent tissues Incidence of subacute bacterial endarteritis is low until patients are in their teens and the highest in cidence is in the third decade However incidence of in fection in young children is not entirely negligible and difficulty of operation is increased with age Rapidity of recovery of young children from the operation is aston ishing

failure may not eventually appear A woman 53 and a girl 16 both succumbed to bacterial endarteritis following years of normal health despite the cardiac lesion A woman 46 died within two weeks after development of heart symptoms of dyspnea and palpitation She had been



Fig 69—D

told early in life that she had a heart disorder but it had never bothered her before

These case histories emphasize two opposing arguments concerning surgery Analysis of the world literature showed that 90 per cent of patients eventually succumb to the cardiac lesion Those who were alive at 17 years of age averaged 35 years at death At least 40 per cent of these patients died of subacute bacterial endarteritis and

most of the remainder died of congestive heart failure Spontaneous rupture of the pulmonary artery or the ductus occurred in a few instances The average age of the authors entire series of 51 patients is less than 25 years and the oldest patient died at 58 It is true that most of these patients were found in a children s clinic but the authors made considerable efforts to find adult cases with no great success These data force reconsideration of a conservative attitude toward what might seem radical surgery

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Congenital Patent Ductus Arteriosus Evaluation of Surgical Treatment George E Burch (Tulane Univ) states that physiologic studies have shown that in patent *ductus arteriosus blood flow from the aorta to the pulmonary artery* rarely is there any flow in the reverse direction This explains absence of cyanosis Blood entering the pulmonary artery returns to the left ventricle without *reaching the peripheral circulation* To compensate for loss of blood in the periphery volume output from the left ventricle must increase This occurs without much change in output of the right ventricle The result is considerable increase in work of the left ventricle left ventricular enlargement *strain and eventual failure The left ventricle* has been found to pump four times the volume of blood expelled by the right ventricle These effects on ventricular work explain the normal axis deviation or mild left axis *deviation and rare right axis deviation in the electrocardiogram* Patent ductus arteriosus is associated with many hemodynamic and other cardiophysiologic manifestations seen in aortic regurgitation and arteriovenous aneurysm

Roentgen signs observed by teleroentgenography fluoroscopy or roentgen kymography easily explained by the disturbed function are (1) greatly increased excursions of the left ventricle (2) increased pulsation of the pulmonary artery (3) *overfilling or engorgement of the* pulmonary conus and pulmonary vessels (4) increased pulsations of the bronchovascular structure particularly *prominent near hilar regions* and (5) *enlargement of the* left ventricle *Changes in hemodynamics also explain the* typical machine like murmur and other murmurs commonly heard in this condition

Burch reviewed most of the available cases in the literature on surgical ligation and found *the mean mortality rate for* many surgeons to be about 8 5 per cent in uninfected ducti This does not represent results that may be expected when a surgeon has had experience with only an occasional case or with many cases *There is no doubt that life ex*

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pectancy in persistent ductu arteriosus is considerably reduced Apparently too mo t patients with uncomplicated ductus arteriosus are spectacularly benefited by ligation However these patients have been followed only tour years and only time will determine exactly what influence operation has on duration of life In presence of superim posed bacterial endarteritis the mortality rate in untreated cases is approximately 100 per cent but ligation has re duced this to less than 50 per cent after a follow up of about one year Therefore ligation should be recommended and urged if the patient has associated endarteritis The same is true in patients with progressive cardiac damage and decompensation or patients with definite impairment of mental and physical development One would nevertheless hesitate to recommend or as ume respon ibility for opera tion in a patient who has patent ductus without impair ment of health Dolley and Jones found the operation easier to perform in children aged 4 5 and 6 If this proves true then age will influence considerably the time at which operation should be recommended

It is conceivable that in the future the operation will usually be recommended a soon as a patent ductus is dis covered No such recommendation can be made now with operative mortality averaging 8 5 per cent and being even greater in average hands Until surgeons have developed a relatively safe procedure and results can be predicted preoperatively with greater certainty operation should be reserved for cases with the special indications enumerated

Poor re ults following ligation may be attributed to (1) failure to find the ductus (2) ligation of the wrong vessel (3) wound sepsis (4) hemorrhage (5) associated cardio va cular abnormalities (6) incomplete ductus obliteration

Occlusion of Infected Patent Ductus Arteriosus with Cellophane Fred R Harper (Denver Colo) and Murray L Robinson (Burlingt n C lo) report a case of patent ductus arteriosus in a wom n 28 complicated by long tanding severe subacute bacterial endocarditis

(8) Am J S g 64 94 9 M 1944

The patent ductus arteriosus was occluded by ligating it with two silk ligatures and then wrapping cellophane loosely around it. Postoperative course demonstrated the fact that the cellophane was responsible for the final complete occlusion of the patent ductus arteriosus. For the first two weeks the murmur and symptoms disappeared only to reappear and persist until 2½ months had elapsed from the time of operation. The murmur and symptoms then completely disappeared and the patient had remained entirely well 1½ year after surgery. The cellophane was thought to be responsible for the final complete and permanent occlusion of the patent ductus arteriosus.

Effort Syndrome

Neurocirculatory Asthenia. John A. Reisinger examined 50 men with symptoms referable to the circulatory system which they alleged began during military service or soon after discharge. Medical records showed that these men had been examined and received treatment during the 12–34 years since alleged onset. No patient was included who exhibited signs of cardiovascular disease other than systolic murmurs, minor electrocardiographic changes and various circulatory manifestations not considered evidence of organic damage. Many diagnoses had been made, including tuberculosis, hyperthyroidism, myocarditis, mitral insufficiency, angina pectoris, functional heart disease, neurocirculatory asthenia, neurasthenia and anxiety neurosis. None of the diagnoses implying organic disease could be sustained, yet the patients were incapable of normal exertion without symptoms suggesting circulatory insufficiency. They manifested physical unfitness which could not be accounted for by auscultation of the heart or by any other methods of examination and for want of a better designation their condition was classified as "neurocirculatory asthenia." This term is generally accepted in the United States to label the condition described as irritable heart of soldiers and effort syndrome. Neurocirculatory asthenia is an ill defined syndrome of unknown cause or causes characterized by manifestations permitting considerable latitude for diagnostic interpretation. There is a

(9) M B ll V t Adm 0 8 20 J 1 1943

growing trend to place this disorder among psychosomatic diseases To some examiners the manifestations are those of psychoneurosis usually of anxiety type and many patients with neurocirculatory asthenia also have a psychoneurosis yet the relationship is not clear Furthermore a distinction seems possible between these patients and those who have no circulatory disability but fix their anxieties on the heart usually episodically

Ballistocardiographic Studies of Draftees Rejected for Neurocirculatory Asthenia Isaac Starr (Univ of Pennsylvania) examined with the ballistocardiograph 58 persons rejected for neurocirculatory asthenia They had first been rejected by their draft boards for cardiovascular defects on re examination diagnosis of neurocirculatory asthenia had been made

In 41 instances the ballistocardiograms confirmed the diagnosis of neurocirculatory asthenia for these rejectees

CIRCULATION OF 41 REJECTEES FOR WHOM DIAGNOSIS OF NEUROCIRCULATORY ASTHENIA WAS CONFIRMED

	C s	
Results after 15 min rest horizontal		
Amount of circulation (% deviation from normal shown in parenthesis)		
Hypokinemic (less than —22)	0	
Normokinemic (between —22 and +22)	4	10
Hyperkinemic (+22 to +44)	6	15
(+45 to +66)	11	26
(+67 to +88)	7	1[illegible]
(+88 to +110)	[illegible]	15
(over +111)	5	1[illegible]
Tremor prevented estimate of circulation	2	5
Response to arising		
Circulation increased abnormally	10	24
Circulation diminished abnormally	0	
Pulse rate changed abnormally	4	10
Systolic pressure changed abnormally	9	22
Diastolic pressure changed abnormally	1	2
Tremor ruined vertical ballistocardiogram	[illegible]	15

showed abnormality of the amount of circulation when they were at rest or after rising (see Table) Five persons showed abnormalities of pulse rate or blood pressure but normal circulation and their conditions were considered

(1) W M d 5 15 1 2 M h 1944

to be borderline For three men diagnoses other than neurocirculatory asthenia were preferred In six nothing abnormal was demonstrated and these were considered fit for service Three obese subjects could not be tested

The ballistocardiogram provides objective evidence of abnormality in most persons with a diagnosis of neurocirculatory asthenia It should be of value in the detection of malingerers and should aid in the more difficult decisions concerning fitness for service The preferred view of the nature of the fundamental abnormality present in neurocirculatory asthenia is that it is a maladjustment of the circulation i e inability to adapt it to the needs of the moment

Hypertension

Medical Use of Thiocyanates in Treatment of Arterial Hypertension R F Forster II (Univ of Pennsylvania) presents a detailed review of the literature The pharmacodynamic actions of thiocyanate in arterial hypertension have been reported to affect (1) the central nervous system by sedation and irritation of the anterior horn cell (2) the muscle causing paralytic action and stimulation of smooth muscle (3) blood and vascular organs through decreased viscosity vasodilatation cardiac depression blood cholesterol depression respiratory stimulation and hypotensive and hypertensive effects (4) mucous and endocrine glands (5) kidney exhibiting diuretic action and (6) liver with depression of liver metabolism

The hypotensive effect of thiocyanate has been in question since Pauli in 1903 first suggested use of the drug in treatment of hypertension Goldblatt found that a toxic level was needed to produce a blood pressure fall in hypertensive dogs Grollman *et al* found no significant blood pressure fall in rats with oral dosage Barker and Davis demonstrated that sympathectomy sensitized the patient to thiocyanate so that a small dose would create the same hypotensive effect after operation that a large one would before Hamilton found no significant drop in blood pre

(7) Am J M S [illegible] 1943

sure in dogs treated with thiocyanate Search of the literature revealed no report of a hypotensive action in a laboratory animal except when it was quite toxic However most clinical authors believe that there is a definite hypotensive effect in a large percentage of cases of arterial hypertension A blood pressure increase terminating in death has been observed in animals poisoned with thiocyanate

Toxic effects of thiocyanate that have been reported in patients include direct effects of moderate severity with low blood levels (12 mg per 100 cc or less) such as weakness and fatigue dermatitis and nausea direct effect of great severity with greater than therapeutic blood levels including gastric hemorrhage purpura decreased libido nervousness bloody diarrhea hallucinations and other mental symptoms neuritis exfoliative dermatitis pyrosis anorexia and nausea acute symptoms due to sensitivity to thiocyanate Besides these direct effects indirect toxic effects due to the fall in blood pressure have been reported *particularly anginal attacks*

[Is it not possible that the thiocyanate do more harm to the body cells over a period of time than does the state of hypertension itself?—Ed]

According to present knowledge actual dosage of thiocyanate in arterial hypertension is not as important as blood level Goodman recommends 0 3 Gm per day Griffith recommends 0 2–0 4 Gm per day initially and a blood thiocyanate level taken by at least the end of the first week The following doses should be entirely regulated by the blood level Griffith s micromethod is the most practical for frequent blood level determination The level of 15 mg per 100 cc should never be exceeded Barker recommends a level between 5 and 6 mg per 100 cc at first If there is no benefit this should be raised to 8–12 mg per 100 cc Levels of 40–60 mg per 100 cc without untoward symptoms have been observed The drug is administered orally and sodium thiocyanate and potassium thiocyanate are used almost equally in reported cases No beneficial effects appear for at least a week Effect may last two months

after the drug is stopped The drug may be retained until about the sixth day Dogs retain toxic effects for about two weeks Thiocyanate is not evenly distributed to all parts of the body but does reach an equilibrium with the body fluids in about two hours It is not distributed to the cerebrospinal fluid

Griffith advises use of thiocyanate only in selected cases of hypertension with some degree of capillary mobility or reducible spasm This is in contrast with general opinion which seems to be that thiocyanate should be used in any hypertensive individual unless contraindicated There is disagreement about contraindications but kidney disturbances heart damage cardiac decompensation and general inflammatory conditions have been given as contraindications Patients with renal retention and poor clearance are more likely to radical toxic effects

Theories on the hypotensive action of thiocyanate in the hypertensive patient include (1) decreased cardiac output through cardiac depression the endocrines and decreased venous return (2) decreased peripheral resistance through vasodilatation decreased blood viscosity and removal of calcium deposits (3) decreased blood volume and (4) miscellaneous including an effect on tissue oxidation depression of liver metabolism decrease in guanidine bases and increase in nitrogen and sulfur excretion In general sex age retinal lesions urinary findings myocardial damage orthodiagram cytologic findings and serology show no relation to the hypotensive effect Actually some of the subjective effects for which thiocyanate is given also appear to be caused by it

[Griffith believes that increased capillary fragility is a contraindication to use of the thiocyanates in hypertension.—Ed]

This review reveals that most clinical workers believe that thiocyanate has a definite hypotensive effect in the patient with arterial hypertension but this has not been demonstrated in the laboratory The mechanism by which this clinical blood pressure drop occurs is not known It is hoped that a complete statistical analysis will be done to prove this suspected hypotensive effect A satisfactory

method for administration of thiocyanate has been suggested by Barker which will give minimal toxicity if handled correctly Thiocyanate should never be given without blood level determinations It is not a blanket cure all for hypertension and should be used only in selected cases and where no contraindication exists Any relief of subjective symptoms bears minimal relation to the blood pressure drop

Urologic Factors Influencing Hypertension Basil A Hayes and J D Ashley report a urologic study of 55 consecutive patients with so called medical hypertension and no particular urologic symptoms who applied for treatment on the medical service of the University of Oklahoma Hospital Examination consisted of special inquiries regarding bed wetting toxemias of pregnancy operations and previous history of urinary tract disease followed by routine cystoscopic examination in which specimens were taken from each kidney and indigo carmine determinations and pyelograms made

There were 22 men and 33 women Average age was 47 among the men and 48 among the women Duration of symptoms for the women varied from a few months to 20 years and averaged 4 years Among the men the shortest period was six months and the longest according to a patient 29 all his life Average for the men was five years Average systolic pressure among the men was 209 mg and diastolic 126 8 Among the women systolic pressure was 202 mg and diastolic 120 5 The highest systolic pressure in the whole group was 300 the lowest 160 The highest diastolic pressure was 160 and the lowest 80 Of 17 men who gave a family history 9 reported cardiovascular or renal disease either in father mother or older brother or sister 8 gave no such history Of the women who gave a family history 13 gave a positive and 11 a negative history

Only six patients gave a history of scarlet fever and from the findings in these cases it would appear that scarlet

(3) J U I 50 366 373 S p t 1943

fever played little or no part in development of the hypertension The history showed a high percentage of bed wetters and of chills and fever during childhood Twenty six of the 33 women had had a toxemia of pregnancy or a pelvic operation or both Cystoscopic examination showed that 54 5 per cent of the whole group had obstructive lesions of the lower urinary tract Approximately 60 per cent showed various changes in the upper tract commonly ascribed to back pressure Other lesions found were renal calculi ureteral calculi renal cyst polycystic disease duplication of ureters and pelves and ptosis of one or both kidneys In both men and women nearly all these kidneys had intrarenal pelves i e 19 among the men and 27 among the women Three were extrarenal three were mixed types and three were not noted as the pyelograms were studied The authors believe that the intrarenal pelvis is more likely to eventuate in hypertension than hydronephrosis if there is back pressure put on it from below

The lesions found in this study were sufficient in number and importance to suggest urologic examination of all patients with hypertension not only for improvement of the urinary tract but in an attempt to correct etiologic factors causing hypertension

Thoracolumbar Sympathectomy in Essential Hypertension J William Hinton (New York City) states that classification of hypertension cases is difficult Schroeder and Steele divide such cases into four organic groups (1) renal disease—(a) glomerulonephritis (b) urinary obstruction (c) polycystic kidneys (d) pyelonephritis (e) aberrant arterial supply to the kidney and (f) Wilms s tumor (2) diseases of the nervous system—(a) brain tumors and (b) diseases such as bulbar poliomyelitis (3) endocrine diseases—(a) basophilic tumors of the pituitary (b) adrenal tumors and (c) ovarian tumors i e arrhenoblastoma (4) arterial disease such as generalized arteriosclerosis A fifth group of unclassified cases probably fall chiefly in groups 2 and 3 Hypertension cases have been

(4) N w Y k St t J M 1 44 884 8 8 Ap 15 1944

classified for clinical correlation of end results according to severity of eyeground changes (1) arteriolar constriction only—with normal renal function (2) tortuosity and nicking of veins at crossings—with normal renal function (3) marked arteriolar changes associated with retinitis with hemorrhage or exudate or both—with impaired renal function (4) malignant hypertension because of papilledema with hemorrhage and exudate—with markedly impaired renal function

Hinton performed thoracolumbar sympathectomy in 40 patients 1 in group 1 4 in group 2 15 in group 3 and 20 in group 4 Ten patients had been refused operation elsewhere Among the 20 patients in group 4 there were three deaths two from myocardial insufficiency one of which occurred on the thirteenth day and the other on the third day after the first stage operation The third death was due to filling of a tuberculous cavity which had been present 20 years

The type of operation used should be taken into consideration in appraising results of surgical treatment of hypertension Operations which come closest to complete denervation of the splanchnic bed should yield best results

Patients with essential hypertension are entitled to the benefit of a consultation but this should be held with an open mind and the patients should have the facts honestly presented so they may make their own decision regarding operation A case is presented which illustrates the difficulty of presenting a clear picture of the problem to the patient

Woman 44 married with no children had a normal blood pressure in October 1941 Six weeks later she consulted a physician for a condition unrelated to the cardiovascular system who found blood pressure of 2[illegible]5 120 She then consulted a gynecologist for another complaint he advised her (six months after onset of hypertension) to seek an opinion as to advisability of thoracolumbar sympathectomy Hinton found that she had *essential hypertension group 2 with some cardiac enlargement* and blood pressure 200 130 The facts were frankly presented to the patient her husband and the referring gynecologist and the patient decided to have the opera

tion By chance she met a well known cardiologist shortly before entering the hospital and he strongly advised against operation Since his advice was not solicited the patient asked him how many patients he had been operated on for essential hypertension and what type of operation they had had to which his reply was that he had seen none The patient stated that perhaps her judgment might be as good as his as to what course she should pursue Nine months after operation examination showed blood pressure of 132/90 entirely normal heart tones and minimal evidence of peripheral vascular change Fluoroscopy showed slight enlargement of the left ventricle otherwise the heart seemed normal The electrocardiogram was well within normal limits and did not even show a left axis deviation

Thoracolumbar sympathectomy has produced reversible changes in kidney function as demonstrated by blood chemistry Papilledema resulting in blindness has been relieved with return of normal vision Patients totally disabled over long periods one for 4½ years have been restored to normal earning capacity Patients in group 4 should not be considered hopeless as excellent results are frequently obtained by thracolumbar sympathectomy

Essential Hypertension In discussing surgical treatment of essential hypertension William P E Berwald (Rochester N Y) and Kenneth D Devine (Mayo Clinic) state that the rationale for sympathectomy in this condition is predicated on the following results of the denervation (1) relaxation of a large portion of the vascular bed i e blood vessels of the lower extremities and the splanchnic bed (2) postural fall in blood pressure which always follows sympathectomy but which usually disappears in months or a few years (3) increased blood supply to the kidneys and (4) decrease in amount of adrenalin secreted as a result of excitement fear and other vasomotor stimuli The first two results mentioned are irrefutable The last two are open to discussion although there is a growing body of evidence to support them

One criterion for operation is age—50 or under Age should be calculated physiologically rather than chronologically for obviously it would be unwise to deny a slightly

(5) Am J Surg 64 38 384 J 1944

older patient with elastic arteries the benefit of operation *Operation should be refused to patients who fail to respond in any measure at all to the sodium amytal and sodium nitrite tests*

The sodium nitrite test consists of giving ½ gr sodium nitrite every half hour for six doses and recording the blood pressure every half hour for five hours The room is darkened visitors are barred and nursing care is minimal The sodium amytal test is similar except that 3 gr is given every hour for three doses

Evaluation of these tests in 29 patients showed that if under the sodium nitrite test diastolic pressure is reduced 20 mm Hg or more the chances are that 64 per cent of such patients will have a good final result Similar lowering of diastolic pressure with sodium amytal suggested that 60 per cent of patients will have a good final result The lowering of systolic blood pressure by these two drugs is a less accurate criterion of end results

Patients with advanced cardiac and renal damage should be refused operation Obese individuals should lose considerable weight before surgery is attempted No impressive relationship was observed between retinal vessel sclerosis and response to sympathectomy in this series

Of 29 patients who underwent sympathectomy 2 died 1 as the result of operation Average preoperative blood pressure was 244/127 and average blood pressure about 10 months following sympathectomy was 166/112 Average reduction in systolic pressure was 78 mm and in diastolic pressure 15 mm Average systolic drop under sodium nitrite and sodium amytal was 42 7 mm and average diastolic drop was 18 2 mm These figures show that sympathectomy enhances the results of sedative and vasodilating drugs so far as the systolic reading is concerned but falls slightly short of their effect as regards the diastolic value This deduction is predicated on the administration of rather large doses of each drug i e 9 gr sodium amytal and 3 gr sodium nitrite within separate three hours periods Obviously these doses would be rather disastrous clinically

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Of 29 patients who underwent sympathectomy 2 died 1 as the result of operation Average preoperative blood pressure was 244/127 and average blood pressure about 10 months following sympathectomy was 166/112 Average reduction in systolic pressure was 78 mm and in diastolic pressure 15 mm Average systolic drop under sodium nitrite and sodium amytal was 42 7 mm and average diastolic drop was 18 2 mm These figures show that sympathectomy enhances the results of sedative and vasodilating drugs so far as the systolic reading is concerned but falls slightly short of their effect as regards the diastolic value This deduction is predicated on the administration of rather large doses of each drug i e 9 gr sodium amytal and 3 gr sodium nitrite within separate three hours periods Obviously these doses would be rather disastrous clinically

It is considered that good results have been obtained when systolic pressure is lowered 50 mm or more and diastolic pressure 20 mm or more Objectively there has been a good response in 18 patients and poor response in 10 Most patients experienced subjective improvement

Effect of Surgical Operations on Blood Pressure was studied in 208 cases by J D Adamson and Sara Dubo (Univ of Manitoba) Twenty eight patients with hypertension who did not have operations were followed also during hospitalization Definite reduction in blood pressure occurred in all cases and was similar in the group with and without operation it was greater in actual millimeters of mercury and in percentage in individuals with high blood pressure Actual and percentage reductions in systolic and diastolic blood pressures were comparable to those attributed to specific operations on the sympathetic nervous system Subjective symptoms also tended to disappear during hospitalization whether or not operation was performed

The authors do not conclude from this evidence that sympathectomy should never be performed for hypertension They suggest however that alleged specific effects must be measured against known nonspecific effects which occur concurrently with all surgical operations Careful and prolonged observation under various conditions must be made before and after sympathectomy before definite conclusions can be drawn

Nonspecific Major Operations and Lumbodorsal Sympathectomy Francisco Roja (Santiago Chile) R H Smithwick and Paul D White (Massachusetts Genl Hosp) [7] compared the effects on blood pressure of (1) nonspecific operations (100 cases) and (2) lumbosacral sympathectomy in 100 hypertensives Reductions of less than 5 per cent of initial systolic or diastolic pressure were considered as no results reductions between 5 and 25 per cent as moderate and reductions over 25 per cent as pronounced

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Blood Pressure of Patients Who Had Another Operation Besides Lumbodorsal Sympathectomy

P		B.P.
1	3/23/43	190/120
	Ovariectomy	
	3/24/43	
	4/7/43	200/90
	Lumbodorsal sympathectomy	
	6/1/43	
	7/10/43	150/90
	12/13/29	150/90
	Cholecystectomy	
	12/16/29	
	4/13/41	224/114
	Lumbodorsal sympathectomy	
	6/3/41	
	6/28/41	140/80
3	11/4/42	240/160
	Right lumbodorsal sympathectomy	
	11/14/42	
	Cholecystectomy	
	11/28/42	210/110
	Left lumbodorsal sympathectomy	
	12/26/42	
	12/28/42	170/90
4	8/26/43	200/110
	Thyroidectomy	
	8/27/43	
	8/29/43	180/90
	Lumbodorsal sympathectomy	
	9/25/43	
	10/14/43	130/90
	5/10/43	160/100
	Right lumbodorsal sympathectomy	
	5/13/43	
	Cholecystectomy	
	5/25/43	
	6/5/43	170/100
	Left lumbodorsal sympathectomy	
	6/19/43	
	7/13/43	120/80
6	5/30/38	190/120
	Hysterectomy	
	6/8/38	
	9/18/38	180/120
	Lumbodorsal sympathectomy	
	10/5/38	
	10/15/38	140/100

Differences in immediate postoperative results were quite apparent group 1 no response—systolic 49 per

cent and diastolic 60 3 per cent pronounced reduction—systolic, 2 per cent and diastolic 12 6 per cent group 2 no response—systolic 3 3 per cent and diastolic 8 8 per cent pronounced reduction—systolic 72 3 per cent and diastolic 53 5 per cent Six months or more later (average 10 months) the differences in reduction were even more striking group 1 no response—systolic 82 7 per cent and diastolic 86 per cent pronounced reduction—none group 2 no response—systolic 9 6 per cent and diastolic 7 6 per cent pronounced reduction—systolic 62 3 per cent and diastolic 56 3 per cent

Comparisons of reduction of blood pressure after the first and second stages of lumbar sympathectomy showed that reduction after the first stage was similar to that seen after any other operation Not until after the second stage is a real reduction of blood pressure noticeable

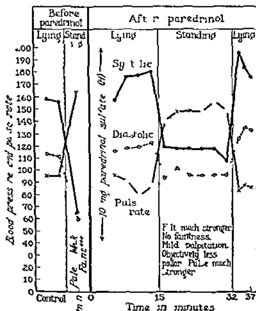
As a final analysis of the specificity of Smithwick s two stage operation the authors analyzed the blood pressure data of patients who had not only sympathectomy but another operation before or between the two stages of sympathectomy (see Table) The authors conclude that Smithwick s technic is specific since in most cases blood pressure was markedly reduced after long observation This specificity is further demonstrated by the fact that definite results do not occur until after the second stage of the operation

[It seems to me that these authors—advocates of the two stage radical lumbodorsal sympathectomy in hypertension—have made their point that this operation reduces blood pressure more appreciably than any ordinary operation with subsequent bed rest etc—Ed]

Circulation in Man in Certain Postures before and after Extensive Sympathectomy for Essential Hypertension Effect of Certain Mechanical Agents and Paredrinol on Blood Pressure and Pulse Rate was studied in 10 patients by Earl F Cambill Edgar A Hines Jr and Alfred W Adson (Mayo Clinic)

(8) Am. H t J 7 381 39 M h 1944

Use of a tight abdominal binder was of considerable benefit in counteracting excessive orthostatic hypotension and tachycardia postoperatively That the binder had little effect pre or postoperatively in cases in which orthostatic hypotension and orthostatic tachycardia were not great but did increase blood pressure and slow the pulse rate after



F 0 —Effect f 10 mg p edr 1 lf t bcut eo ly n th tat blood p d p l e i ft ympath t my

operation when these phenomena occurred suggests that the defect responsible for this condition lies at least partly within the abdomen Cuffs tightly applied above both knees to cut off circulation to the legs tended to elevate blood pressure and slow pulse rate This effect was greater after than *before sympathectomy* and was *greatest after operation* among patients with most severe orthostatic hypoten

sion and tachycardia. Combined use of an abdominal binder and thigh cuffs had a greater blood pressure raising and pulse slowing effect than either procedure alone. The effect was due chiefly to factors other than the discomfort induced by these agents. Exercise of the legs did not produce a conclusive effect on orthostatic blood pressure and orthostatic pulse rate.

Paredrinol sulfate definitely raised blood pressure postoperatively in the horizontal and erect postures and alleviated most symptoms which otherwise resulted when patients were erect. It reduced somewhat the amount of orthostatic decrease in blood pressure (Fig 70). The authors conclude that the drug may be helpful in counteracting excessive degrees of orthostatic hypotension when patients begin to walk soon after sympathectomy.

HYPOTENSION

Orthostatic Tachycardia and Orthostatic Hypotension Defects in Return of Venous Blood to the Heart. Alexander R. MacLean (M.C., U.S.N.R.), Edgar V. Allen (M.C., A.U.S.) and Thomas B. Magath (M.C., U.S.N.R.) made a detailed study of normal subjects and numerous patients with various disorders with respect to standing and recumbent blood pressures, heart rates and Flack tests. Orthostatic defects of venous return are divided into two groups: those in which orthostatic changes are inconsistent and not associated primarily with organic disease and those in which they are consistent and associated with organic changes.

Many syndromes present transient, inconsistent abnormalities of venous return, with remissions and exacerbations which cannot be controlled or foreseen adequately. Investigation of such cases (group 1) in regard to causative factors, contributing disabilities and results of treatment cannot be conducted satisfactorily, although insight may be gained into the nature of the disability. Only when venous return consistently fails in the erect posture can objective experimental studies be conducted with profit.

(9) Am. H[illegible]t J. 27: 145 16 F[illegible]y 1944

Detailed clinical observation is reported on two patients which with previous studies of orthostatic hypotension and tachycardia associated with organic disease demonstrate several important principles. Orthostatic hypotension and tachycardia are in a secondary sense disorders of venous return. The defect becomes evident shortly after erect

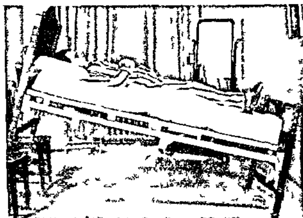


Fig. 1.— [illegible]

posture is attained and conversely adequate circulation and a normal heart rate and blood pressure immediately follow resumption of the recumbent position. The site of this disorder appears to be the capillary venous bed of the lower extremities for orthostatic symptoms and signs and positive Flack reactions are abolished when lower extremities are separated from the general circulation by cuff inflated about the thigh. The circulatory defect caused by inadequate venous return in the erect state is either a direct result of pooling of abnormal quantities of blood in the lower extremities or a result of a rapid transudation of circulating fluid into the tissues of the lower extremities. Rapidity of onset of the deficiency when the upright posi

sion and tachycardia Combined use of an abdominal binder and thigh cuffs had a greater blood pressure raising and pulse slowing effect than either procedure alone The effect was due chiefly to factors other than the discomfort induced by these agents Exercise of the legs did not produce a conclusive effect on orthostatic blood pressure and orthostatic pulse rate

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Hypotension

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Many syndromes present transient inconsistent abnormalities of venous return with remissions and exacerbations which cannot be controlled or foreseen adequately Investigation of such cases (group I) in regard to causative factors contributing disabilities and results of treatment cannot be conducted satisfactorily although insight may be gained into the nature of the disability Only when venous return consistently fails in the erect posture can objective experimental studies be conducted with profit.

(9) Am Heart J 27 145 161 February 1944

of salt appears to result in definite symptomatic and objective changes which are reversible and correspond to an increased volume of circulating blood and increase of extracellular fluid of the lower extremities

Hyperthyroidism

Heart and Hyperthyroidism Lewis M Hurxthal (Lahey Clinic) presents three illustrative cases The heart in hyperthyroidism is overactivated because of the increase in metabolism which increases the circulation rate and because the thyroid hormone increases metabolism of the heart muscle itself This overactivity is helpful in diagnosis but must be distinguished from that in mitral stenosis About 10 per cent of all patients with hyperthyroidism develop fibrillation It is usually transient but becomes permanent in about 5 per cent of cases Auricular fibrillation may occur without great toxicity but in the average patient with fibrillation the goiter is toxic Twenty to 50 per cent of patients with fibrillation develop congestive failure The heart fails in hyperthyroidism because it cannot carry the abnormal load imposed by the overactivity accompanying the disease

The three principles in treatment are (1) to decrease thyroid toxicity which may relieve all cardiac symptoms (2) to increase cardiac function by digitalization if fibrillation is present and (3) to relieve accumulation of fluids by diuretics or tapping

Apparently hyperthyroidism does not cause cardiac enlargement but the heart is dilated when there is congestive heart failure *In about 50 roentgenograms of patients* with hyperthyroidism for over four years and of patients who had the disease less than six months matching age for age and sex for sex no difference was found in size of the heart in the two groups

Thyrotoxicosis as Sole Cause of Heart Failure William B Likoff and Samuel A Levine (Peter Bent Brigham Hosp) analyzed all cases in which a subtotal thyroidecto

(1) P I t t P tgr d M \ \ th Am 1 43 pp 55 58
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tion is assumed and instantaneous recovery in the recumbent state suggest strongly that the defect is the result of pooling of blood in the capillary venous bed itself

Variations of potential of venous return occur in normals and in patients with various disorders A persistently maintained recumbent state enhances defects of venous return when the erect posture is assumed A persistently maintained erect or semierect posture definitely lessens orthostatic changes in pulse rate and blood pressure and increases postural vascular stability This improvement in vascular adaptation depends on physiologic factors which are little understood It would appear that part of the postural vascular adaptation depends on physical mechanisms related to shifts of extracellular fluid and changes of blood volume Maintenance of the erect or semierect position favors accumulation of additional extracellular fluid in the legs Frequently among patients treated on the head up bed (Fig 71) appearance of early edema of the lower extremities coincides with lessening of orthostatic signs and symptoms this edema quickly disappears as patients become more active Such an increase of extravascular fluid might well act as a splint of the capillary venous bed of the lower extremities and prevent excess pooling of blood in the erect state Maintenance of erect or semierect position also favors accumulation of blood itself in the legs and volume of circulating blood in upper portions of the body is to that extent reduced This should stimulate recovery mechanisms as would an actual hemorrhage by reduction of capacity of the vascular bed by vasoconstriction retention of body fluid and interchange of fluid between tissues and vessels If through such recovery mechanisms volume of circulating blood in the upper part of the body approaches normal then assumption of the recumbent posture would cause additional volumes of blood to gravitate into the circulation from vessels of dependent portions or from extracellular fluids accumulated there

Clinically use of the head up bed and increased intake

In 99 cases with cardiac involvement there was no surgical mortality All but seven of the patients had a one stage subtotal thyroidectomy Surgical mortality in 310 case without heart disease however was 2 6 per cent Hence the authors believe that the so-called severe thyrocardiacs do not require a multiple stage operation and feel that they present less operative risk than younger patients with exophthalmic goiter

It is evident that masked thyrotoxicosis is being overlooked as a cause of heart failure an error that is costly because the condition is curable Absence of other forms of heart disease in the group of 21 patients with congestive failure from thyrotoxicosis was proved by follow up study After an average period of 5 years (longest 10 years) none showed any evidence of organic heart disease There were four deaths during this period all from carcinoma all other patients were essentially well

Psychoneurosis

Psychosomatic Factors in Disorders of the Circulatory System Nolan D C Lewis (New York State Psychiatric Inst and Hosp) believes that emotional disturbances may directly or indirectly affect the cardiovascular system in many different ways In the unconscious or emotionally determined cardiac disorder of everyday life there may be an otherwise important organic lesion on which an emotional fixation with unconscious phobic elaboration has formed or there may be no objective nucleus to account for focalizing of the disorder Some form of fear is usuall in the foreground and the problem tends to be complicated The heart is highly sensitive to emotional excitement and a long period of even mild anxiety renders it irritable and likely to become excited under a relatively slight excess of emotional feeling The pulse may become accelerated by the simple act of taking it Active fear and rage produce palpitation Rage may also produce precordial oppression and is known to have brought on attacks of syncope or angina pectoris Excessive grief may initiate a functional

ms was performed between 1923 and 1941 (see Table) From these data it is apparent that thyrotoxicosis not infrequently is the sole cause of congestive heart failure

Congestive failure is more likely to occur in female with increasing age when the thyrotoxic state is of lon

DATA ON SERIES FROM PETER BENT BRIGHAM HOSPITAL

	No	F	M	Av Age Yr	Av Dur of Thy Mo	A F
Noncardiacs						
Compensated	310	240	70	40	8	22
Decompensated	21	19	2	44	29	8
Severe	8	7	1	45	55	7
Moderate	13	12	1	43	12	1
Total	331	259	72	40	9	30
Cardiacs						
Compensated	39	28	11	53	7	6
Decompensated	39	32	7	52	10	23
Severe	23	19	4	52	9	20
Moderate	16	13	3	52	11	3
Total	78	60	18	53	8	29
Hypertensives						
Compensated	27	19	8	54	8	5
Decompensated	18	15	3	57	11	8
Total	45	34	11	55	9	13
Coronary artery disease						
Compensated	8	5	3	56	7	1
Decompensated	4	4	0	61	10	3
Total	12	9	3	58	8	4
Rheumatic heart disease						
Compensated	4	4	0	43	6	0
Decompensated	16	13	3	44	8	12
Total	20	17	3	44	8	12
Syphilitic heart disease	1	0	1	52	8	0
Grand total	409	319	90	42	9	59

duration and when auricular fibrillation is present No satisfactory explanation was found for the heart failure especially in the noncardiac group Vitamin B deficiency may be contributory Similarity between symptoms and physical findings in mitral stenosis and thyrotoxicosis may lead *to errors* in diagnosis for even left auricular dilatation on roentgen examination is found in the latter condition

ment These two group probably represent examples of similar reactions in which the original focus or fixation points are principally located in the neurovegetative integrations or in personality maldevelopment where environmental situations release a formerly quiescent disorder Besides undue fatigue on effort symptoms include excessive perspiration palpitation precordial pain sensation of breathlessness headache blurred vision giddiness and sometimes syncope tremors vasomotor instability insomnia and nightmares The heart is rarely enlarged but may show sinus arrhythmia and paroxysmal tachycardia short systolic murmurs are not uncommon

The term nervous heart includes a number of disturbances of cardiac efferent and afferent nerves caused by various conditions whose essential feature is anxiety Symptoms may constitute a part of a neurasthenia hypochondria hysterical substitution or conversion or anxiety neurosis or may exist chiefly as an obsessional focus Efferent disturbances interfere with frequency or force of heart action while afferent disturbances result in increased perception of heart action pain or other annoying sensations These may be combined in the same clinical picture

A real heart disorder may be accompanied by neurotic symptoms As the patient becomes aware of the basic disorder states of apprehension fear and panicky sensations alternating with mild depressions or mental irritability may develop The neurotic person with heart disease may increase the cardiac burden by constant tension or acute emotional episodes These may and often do hasten cardiac failure

Psychic factors are important in essential hypertension Individual emotional elements influencing blood pressure readings benefit derived from rest and mental quiet and aggravation produced by anxiety are well known In addition the type of personality and the whole emotional life situation seem to constitute the setting in which this complex physically expressed disorder develops Patients with

disorder with altered valve action Anxiety disappointment and grief alter heart functions and contentment and peace of mind favor its healthy action

The heart may respond to emotion or excitement in one of two ways (1) Sometimes an emotional shock will retard heart beat until partial or complete syncope is produced This faintness is usually accompanied by temporary bradycardia (2) In most emotional situations heart rate increases often reaching 120–150 pulsations per minute This may or may not be accompanied by distressing thoracic or other sensations Tachycardia may become an outstanding symptom in the following emotional settings (1) as a continuous expression of a constant fairly active internal unconscious conflict which sometimes has been satisfactorily rationalized (2) periodically as part expression of the memory of a former emotional situation or shock (3) during nightmares or fright dreams the patient awakening during the attack Respiratory symptoms and vasomotor phenomena often accompany emotional disturbances of the heart and palpitations and arrhythmias are frequently expressions of tachycardia of short duration The chief importance of these symptoms in nervous persons is that they may and usually do become foci for phobic elaborations which in turn enhance and increase the disagreeable symptoms

Neurocirculatory asthenia or effort syndrome brought into the foreground during World War I is characterized mainly by irritability of heart action and increased susceptibility to fatigue in which no definite pathologic lesion or underlying pathologic process can be discovered to account for the reaction In half the cases of irritable heart in a group of soldiers there were psychoneurotic factors in the family history and other psychoneurotic predisposing elements In about 70 per cent there was a history of constitutional asthenia and there always had been an irritable weakness of innervation of the entire circulatory system Another group seemed to be originally fairly stable but broke down under excessive strain and excite

plicated by neurotic symptoms and a classic neurosis and careful differentiation must be attempted However in any of these situations if the disorder reveals obvious emotional components psychotherapy is indicated Psychotherapy skilfully managed practically always helps as a supportive procedure even when the principal disorder is organic and requires other active medical attention

Mental Manifestations in Cardiovascular Disease are described by Eugen Kahn (Yale Univ) Many organic pathologic conditions of the cardiovascular system produce anxiety chronic as well as acute Man can be thrown into anxiety by experiences that primarily have nothing to do with his heart but immediately lead to manifestation of cardiac symptoms This apparently clear distinction is not completely water tight Anxiety manifestations in organic cardiovascular disease vary considerably from individual to individual There are seriously afflicted cardiac patients with little if any anxiety on the other hand there are individuals who on the basis of outspoken vasomotor instability suffer severe anxiety attacks in response to seemingly trifling experiences which may however have particular significance for these individuals

Clinically patients may be divided into those without and those with organic cardiovascular disease The first group includes originally anxious and tense persons who under emotional stress may develop all manner of symptoms simulating cardiovascular disease [These cases are classified in the new specialty of psychosomatic medicine —Ed] The commonest are high blood pressure (usually systolic only) tachycardia pain in the heart region urinary frequency weakness headaches and multiple complaint In this group are many passive anxious persons who are thrown out of gear for a long time and perhaps permanently when they note their first extrasystole with development of chronic hypochondriacal concern centering around the heart There are also active anxious and tense individuals who are able to control their anxiety to a

(4) C t M J 83(85 Oct 1943

hypertension while apparently friendly and self controlled have anxiety and strongly repressed aggressiveness beneath the surface This repressed hostility which is denied a free natural outlet creates an extreme psychic tension, expressing itself in heightened arterial pressure

Patients who *develop anxiety reactions* obviously need organized and systematic psychotherapy When this is not available reassurance accurate information and suggestive therapy are helpful and often successful Through simple explanation and assurance high blood pressure in an emotional patient may *drop 20–30 points in a few minute* When a severe or serious heart lesion is accompanied by a superimposed neurosis psychotherapy is urgently indicated since it may not only relieve the fear and emotional tension but thus indirectly aid the organic condition and *prolong life* Among *psychotherapeutic methods* used in these cases are explanation of symptoms and persuasion systematic organized suggestion hypnosis *conversation* method or spontaneous word catharsis (psychologic re education) and psychoanalysis

Lewis stresses that *the first concern of any individual* is to continue to survive in his particular environment Cardiovascular conditions constitute a *serious threat to* survival which the organism attempts to meet Moreover human beings are equipped with affective or emotional mechanisms outside conscious awareness which are not influenced greatly by logical thought that dominates other *activities These emotional dynamic processes influence* and in certain situations dominate and even determine pathologic processes to a *marked degree* Many cardiovascular no ophobias are accidental and temporary other are based on deeply seated need of the personality and are thus *persistent* and more or less resistant to psychotherapy while others are of definite hypochondriacal or of constitutional *significance with incurable aspects with the whole* life dominated by a cardiac error in thinking In these disorders it is often difficult to distinguish between presence and dominance of an organic disease which may be com

they must appreciate their actual capacities and not over exert themselves It is possible in many cases to bring the patients to lead a reasonably appropriate sort of life without allowing them to slip into complete invalidism Understanding and co operation of members of the family are necessary in treatment of patients of both groups

Cardiac Clinics Fear F A Willius says that never before have people been subjected to the stresses strains and uncertainties prevalent today More people are working harder or longer and suffering more severely than ever before Nervous energy expended under conditions of great *stress and strain may greatly exceed that created in the* course of a day particularly when important issues vitally affect the individual his family or business Such circumstances commonly extend over a considerable period and usually are dominated by uncertainty The person worries and a state of tension develops which renders relaxation difficult or impossible and often creates insomnia or fitful sleep Thus maintenance of adequate nervous reserve is *lost in fact all reserve may be dissipated by constant* excessive and futile expenditure of energy A vicious cycle is initiated worry leads to confusion further uncertainties anxieties fatigue and even complete exhaustion The person feels as tired in the morning as he did in the evening when he retired

Exhaustion of nervous reserve conditions a person to the experience of countless abnormal subjective sensations *which when sufficiently marked defy his own rational* interpretation and in turn create new fears Devastating fears are those bringing direct threats to health or life Here the physician encounters a large group with more or less specific complaints referable to various important organs e g the patient with heart consciousness or thoracic pain who fears heart disease the patient with dyspepsia who fears cancer of the stomach the patient with headache who fears brain tumor and the *one with chronic cough* who fears tuberculosis

(5) P St ff M t M Cl 19 179 18 Ap 1944

degree but under pressure respond with cardiovascular symptomatology and sometimes hypochondria A few in this group show vasomotor instability and may ultimately develop hypertension Thus the demarcation between the first and the second group may become indistinct Anxious persons may acquire organic cardiovascular disease and patients with organic cardiovascular disease may display grave anxiety

In the second group with organic disease patients with apparently similar organic pathology react differently according to their disposition and training Certain robust active energetic persons entirely neglect and disregard their disease and may even actively resist any attempt at treatment There are some originally anxious persons who overemphasize and exaggerate the situation and seem even to welcome invalidism There are others in whom the cardiac involvement e g angina pectoris and coronary occlusion brings about serious anxiety of which they do not complain outside of the attacks This anxiety obviously is due to pathologic happenings in the cardiovascular system When blood vessels of the central nervous system are involved cerebral anoxemia with consequent brain damage due to circulatory failure may develop Early symptoms are irritability restlessness and insomnia Later periods of acute confusion and excitement may appear during and after which paranoid features may develop These conditions are often seriously and dangerously complicated by indiscreet use of sedatives

In treatment of mental manifestations in heart disease the person—not the symptoms—is to be treated Even in the second group with organic lesions it remains imperative to treat the person in his situation In the first group no medication is given except mild doses of luminal during attacks of anxiety The real problem is to educate the patients guide them and give them insight into the fact that the cardiac complaints are rooted in anxiety Neither is medication always necessary in the second group These patients need to accustom themselves to a sensible regimen

streptococci Bacterial counts of the air in the pavilions revealed few pathogenic organisms Twenty children with *recent but clinically inactive rheumatic fever* were admitted and visitors wearing masks and free from respiratory infection were allowed in the wards only once a week None of the 20 patients developed respiratory infections or rheumatic activity After they returned home in excellent health their resistance to rheumatic fever appeared to be sustained

As to the hereditary factor if both parents have had rheumatic infection nearly all progeny will become afflicted If one parent is positive and a grandparent on the other side of the family is positive expected incidence is about 50 per cent If both parents are negative but one grandparent of each line is positive expected incidence is about 25 per cent

There is evidence that rheumatic fever is much less frequent and usually milder in the southern states than in the northern temperate zone However transportation to southern climates is not the answer to the problem of rheumatic infection not only because the disease may recur or remain active in such climates but for economic reason When permanent residence in tropical or subtropical climates can be arranged without hardship it appears a *reasonable prophylactic undertaking* Nevertheless it is better for the patient to remain in the north and receive sulfonamide prophylaxis than to move south and receive *no chemoprophylaxis*

Tonsillectomy does not provide prophylaxis and careful surveys have confirmed the absence of any striking benefit by removal of tonsils on the course of rheumatic fever although statistical and clinical data justify removal of tonsils in practically every rheumatic child Difference in mortality rates reported by Kaiser was apparently dependent on removal of tonsils before the initial rheumatic attack

All observers agree that it is desirable to maintain adequate intake of all essential foodstuffs but there is no con

Helping these patients is not simple and no routine measures can be prescribed. The approach must be individualized and the appropriate approach must be sensed quickly. The first procedure entails careful history, detailed cross questioning and obtaining the patient's confidence so that relevant personal matters are discussed frankly. Indifference or attempted haste may completely prevent any clear understanding of the real problem. Thorough physical examination is next, with special emphasis on the outstanding complaint. The verdict that no organic disease exists must be so convincing that the physician is then able to present the facts so that they are intelligible to the patient. Often it is possible to reveal various trains of events which have occurred in specific relation to the patient's personal problem. It is important to explain that various organs may misbehave and yet be normal in structure and free from disease. Various symptoms while real to the patient are nevertheless counterfeit and their importance becomes greatly altered when factual interpretation and proper significance are accorded them. Nervous disorders and organic disease may coexist; this fairly common experience re-emphasizes the importance of complete and thorough examination in every case.

RHEUMATIC FEVER

Prophylaxis in Rheumatic Fever. The most widely held and best supported view of pathogenesis of rheumatic fever is that certain persons, because of hereditary or environmental factors or both, have developed abnormal tissue reaction to hemolytic streptococci. According to Norman H. Boyer (Boston Univ.) prevention of rheumatic attacks therefore is based largely on prevention of hemolytic streptococcic throat infections. Maintenance of proper nutrition and avoidance of fatigue and chilling are primarily aimed at increased general resistance to infection. Hubbard and Griffin instituted open air sanatorium care for rheumatic children with a view to diminishing exposure to hemolytic

(6) New England J. Med. 8 509 515 Ag 194

other cities with subtropical climates Chorea seems less frequent in this area than in eastern population centers No significant variation in seasonal incidence was noted Analysis of temperature rainfall and relative humidity permitted no correlation between these factors and incidence of rheumatic disease Familial incidence was negligible

Two thirds of the patients were born and reared in the Los Angeles area Almost 80 per cent of those born outside California lived there over a year before onset of rheumatic disease These facts tend to discredit the common belief that most patients with rheumatic infection in California are migrants from eastern or northern states The mortality in this series was 9 5 per cent Seven of the deaths were in Mexican two in Negro and six in white children Ten of the fatal cases were in girls and ages were equally divided below and above 10 years Eleven of the 15 children who died were born and reared in Los Angeles while 3 of the remaining 4 had lived in the city for two or more years Two of the three children with subcutaneous nodules were among those who died Eleven deaths were due to extensive myocardial damage with associated valvular lesions and decompensation two to subacute bacterial endocarditis and one to acute osteomyelitis and sepsis One patient with pancarditis died following exploratory laparotomy

Familial Epidemiology of Rheumatic Fever Genetic and Epidemiologic Studies were carried out in 109 households each of which included at least one rheumatic child Detailed results are reported by May G Wilson Morton D Schweitzer and Rose Lubschez (Cornell Univ) At the time of final tabulation of the data 96 per cent of siblings used for pedigree analysis had reached the age span of maximal incidence and 82 per cent had passed it Observation periods ranged from 6 to 20 years and all but 20 families were observed for over 9 years Many families were under observation in the general clinic preceding onset of the first sibling case In most instances all mem

(8) J P d t 24 849 Ap l 581 611 M y 1943

clusive indication that large amounts of vitamin C or any other food substance have any specific beneficial action on prophylaxis or treatment of rheumatic infection

It has been shown that sulfonamides are ineffective and probably harmful in treatment of rheumatic fever but numerous investigations have demonstrated that they are effective in prophylaxis against hemolytic streptococcic infections and hence represent an important advance in control of rheumatic fever The drug should be begun before the patient is discharged following an attack of rheumatic fever because of danger of exposure to respiratory infections in the home Temperature and leukocyte count should be normal after withdrawal of salicylate but there is no need to wait for a normal sedimentation rate Prophylaxis should be continued throughout the year and the drug should be administered five years or longer after an attack of rheumatic infection Although sulfanilamide has been used in most series reported sulfadiazine has been tried recently and may be preferable because of lower toxicity Attempts at prophylaxis with salicylates and with various streptococcic vaccine have not yielded conclusive result but perhaps deserve additional study

Rheumatic Fever and Rheumatic Heart Disease David B Davis and Sidney Kosin (Beverly Hills Calif)

DATA ON ADMISSIONS

Year	Pediatric	Contagious Dis	Total	Rheum Fever Rheum Heart Dis Cases
1936-1937	2 744	2 051	4 795	45
1937 1938	2 312	2 216	4 528	32
1938-1939	2 550	1 991	4 541	38
1939 1940	2 372	1 472	3 844	38
1940 1941	3 157	1 672	4 829	20
Totals	13 135	9 402	22 537	173

present an analysis of 173 cases of childhood rheumatic fever observed over five years at Los Angeles County Hospital (see Table) The relatively low incidence of rheumatic disease in this survey agrees with finding in

(1) J P d t 4 502 513 M y 1944

other cities with subtropical climates Chorea seems less frequent in this area than in eastern population centers No significant variation in seasonal incidence was noted Analysis of temperature rainfall and relative humidity permitted no correlation between these factors and incidence of rheumatic disease Familial incidence was negligible

Two thirds of the patients were born and reared in the Los Angeles area Almost 80 per cent of those born outside California lived there over a year before onset of rheumatic disease These facts tend to discredit the common belief that most patients with rheumatic infection in California are migrants from eastern or northern states The mortality in this series was 9 5 per cent Seven of the deaths were in Mexican two in Negro and six in white children Ten of the fatal cases were in girls and ages were equally divided below and above 10 years Eleven of the 15 children who died were born and reared in Los Angeles while yet the remaining 4 had lived in the city for two or more years Two of the three children with subcutaneous nodules were among those who died Eleven deaths were due to extensive myocardial damage with associated valvular lesions and decompensation two to subacute bacterial endocarditis and one to acute osteomyelitis and sepsis One patient with pancarditis died following exploratory laparotomy

Familial Epidemiology of Rheumatic Fever Genetic and Epidemiologic Studies were carried out in 109 households each of which included at least one rheumatic child *Detailed* results are reported by May G Wilson Morton D Schweitzer and Rose Lubschez (Cornell Univ) At the time of final tabulation of the data 96 per cent of siblings used for pedigree analysis had reached the age span of maximal incidence and 82 per cent had passed it Observation periods ranged from 6 to 20 years and all but 20 families were observed for over 9 years Many families were under observation in the general clinic preceding onset of the first sibling case In most instances all mem

(3) J Pediat, 2 468-49 Vol 381 621 May 1943)

bers of the families were examined and a continuous medical record was kept on each individual In all essential respects these data fulfil the requirements for genetic analysis

Development of statistical equivalents for individual genetic risk and numerical measures of the age risk made it possible to describe case incidence in these families under various conditions in numerical terms It was shown that age and genetic factors described the pattern of intra familial spread of the disease at any time during the life experience of the families On the basis of age and genetic factors the annual incidence of cases during a 20 year period was predicted (Table 1) Of particular epidemio

TABLE 1—CASES PREDICTED AND OBSERVED FOLLOWING ONSET OF PRIMARY CASE

	Both Parents Negative					One Parent Positive				
Age	Siblings Available	Total Cases Expected	Age Factor	Current Cases Expected	Cases Observed	Siblings Available	Total Cases Expected	Age Factor	Current Cases Expected	Cases Observed
0			0 00	—		1	0.50	0 00	—	
1			0 02	—		—	—	0.02	—	
2			0 08	—		2	1.00	0 08	0 08	
3	4	1 00	0 17	0 17		6	3.00	0 17	0.51	
4	6	1.50	0.29	0 44		1	0.50	0.29	0 14	
5	3	0 75	0 44	0.33	1	7	3.50	0 44	1.54	1
6	6	1 50	0.59	0.88	1	8	4 00	0.59	2.36	2
7	5	1 25	0 71	0 89	1	4	2.00	0 71	1 42	1
8	11	2 75	0 81	2.23	2	4	2 00	0.81	1 62	3
9	7	1 75	0 90	1 58	2	6	3 00	0 90	2 70	4
10	11	2 75	0 96	2 64	5	13	6 50	0 96	6.24	17
11	10	2 50	0.98	2 45	3	5	2.50	0 98	2 45	1
12	6	1.50	1.00	1 50	—	7	3.50	1 00	3 50	5
13+	122	30 50	1 00	30 50	26	91	45 50	1 00	45 50	38
Total	191	47 75		43 61	41	155	77 50		68.06	67

logic significance is the agreement between prediction and observation at the time of onset of the primary case and subsequently Although these observations do not exclude operation of other exciting factors which may be responsible for onset of the disease in susceptible children they

do indicate that whatever the factors are they are uniformly operative at all times during the life experience of families Although the average number of genetically susceptible children predicted in these families was finally realized it cannot be concluded that every genetically susceptible child will necessarily develop rheumatic fever

TABLE 2 — Secondary Attack Rates of Susceptible Children in 10[illegible] Rheumatic Families

Age	Children Exposed	Cases at Onset	Av. Yr. of Life Experience	Secondary Attack Rate
Both parents rheumatic				
Birth	18	–	–	–
0	3	–	10.5	–
1	8	–	25.0	–
2	4	1	30.5	3.3
3	4	5	31.5	15.9
4	1	8	27.5	29.1
5	1	6	21.5	27.9
6	1	8	15.5	51.6
7	–	–	12.0	–
8	–	3	10.5	28.6
9	–	4	7.0	57.1
10	–	3	3.5	85.7
11	1	2	1.5	133.3
12	–	–	1.0	–
13+	–	1	0.5	200.0
Total	41	41	198.0	20.7
One parent rheumatic				
Birth	25	–	–	–
0	9	–	17.0	–
1	5	–	36.5	–
	6	2	41.0	4.9
3	5	7	42.0	16.7
4	4	4	41.0	9.8
5	5	9	39.0	23.1
6	3	1[illegible]	32.5	36.9
7	3	10	24.5	40.8
8	–	10	16.0	62.5
9	–	3	9.5	31.6
10	1	5	6.0	83.3
11	–	1	3.5	28.6
12	–	1	2.5	40.0
13+	1	3	1.0	300.0
Total	67	67	312.0	21.5

bers of the families were examined and a continuous medical record was kept on each individual In all essential respects these data fulfil the requirements for genetic analysis

Development of statistical equivalents for individual genetic risk and numerical measures of the age risk made it possible to describe case incidence in these families under various conditions in numerical terms It was shown that age and genetic factors described the pattern of intrafamilial spread of the disease at any time during the life experience of the families On the basis of age and genetic factors the annual incidence of cases during a 20 year period was predicted (Table 1) Of particular epidemio

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0			0 00	—		1	0.50	0 00	—	
1			0 02	—		—	—	0.02	—	
2			0 08	—		2	1.00	0 08	0 08	
3	4	1 00	0 17	0 17		6	3.00	0 17	0 51	
4	6	1.50	0.29	0 44		1	0.50	0.29	0 14	
5	3	0 75	0 44	0 33	1	7	3.50	0 44	1.54	1
6	6	1.50	0.59	0.88	1	8	4.00	0.59	2.36	2
7	5	1.25	0 71	0 89	1	4	2.00	0.71	1 42	1
8	11	2.75	0 81	2.23	2	4	2 00	0.81	1 62	3
9	7	1.75	0 90	1 58	2	6	3 00	0 90	2 70	4
10	11	2.75	0 96	2 64	5	13	6 50	0 96	6.24	12
11	10	2.50	0.98	2 45	3	5	2.50	0 98	2 45	1
12	6	1.50	1 00	1 50	—	7	3.50	1 00	3 50	5
13+	122	30.50	1 00	30 50	26	91	45.50	1 00	45.50	38
Total	191	47 75		43 61	41	155	77 50		68 06	67

logic significance is the agreement between prediction and observation at the time of onset of the primary case and subsequently Although these observations do not exclude operation of other exciting factors which may be responsible for onset of the disease in susceptible children they

city Should further studies of families in different geographic and economic environments reveal a difference in penetrance of the disease methods for control of rheumatic fever would be available Such data are now being collected

If these observations are valid it would appear reasonable to postulate that distributed in the general population are children who are susceptible or insusceptible to rheumatic fever on a genetic basis One may speculate that in a genetically susceptible child the connective tissue system by reason of inherent anatomic or physiologic characteristics manifests the pathologic changes which characterize the rheumatic process It is also conceivable that susceptibility specific or nonspecific in the immunologic sense may be a genetic character This inherent susceptibility need not necessarily be considered specific for rheumatic fever

The genetically susceptible individual manifests or develops the disease by the average age of 6 years Interpretation of the age expression of rheumatic fever depends on whether it is postulated that expression of the disease is inevitable or that nongenetic factors are necessary for its development Possibly both genetic and nongenetic factors are operative If nongenetic factors are solely responsible for onset of rheumatic fever among susceptible children the age expression of the disease may reflect the interval of time necessary for its development This may be as short as one year but is more often six years It is then reasonable to speculate that the rheumatic process is the result of the response of susceptible tissues to specific or nonspecific agents which need not necessarily be bacterial

These studies indicate that the most important factor in pathogenesis of rheumatic fever is genetic susceptibility of the host Additional studies are needed to determine whether every susceptible individual develops rheumatic fever Final interpretation of the age expression of rheumatic fever should reveal factors responsible for onset of the

The findings in this study permit a rational description of rheumatic fever as it affects attacked families In familie selected because of presence of at least one rheumatic child distribution of cases follows the general laws of inheritance Frequency of cases is consistent with the hereditary mechanism of a single autosomal recessive gene Predic tions based on the hereditary mechanism postulated were finally realized and therefore it may be concluded that susceptibility to rheumatic fever is hereditary Since the e genetic predictions represent average estimates of the num ber of genetically susceptible individuals present it ma also be stated that in these families all genetically suscep-tible children developed rheumatic fever Accepting su ceptibility of the host to be on a genetic basis nonrheuma tic siblings in the family may be considered insusceptible Age and genetic factors were adequate to describe the intrafamilial pattern of spread for onset of the disease at pecific calendar years over 20 years at epidemiologic points of analysis and among families of certain environ mental groups

Rheumatic fever was not found to exhibit the u ual characteristics of a communicable disease The observation are not consistent with operation of any specific bacterial agent No evidence was obtained to support the postulate that contact with an active or quiescent rheumatic indi vidual was responsible for onset of the disease in u ceptible children If bacterial agents are responsible for onset of rheumatic fever they would appear to be ubiqui tous The possible role of other environmental factors such as climatic or dietary factors was not entirely excluded If operative these were apparently uniformly available or effective Recent studies have suggested that differences in vitamin requirements may be on a genetic basis this aspect is under investigation

Specific statements as to etiology of rheumatic fever and its control cannot be made on the basis of data presente l Comparable ob ervations would be expected and have been obtained in a similar urban clinic population in another

rehabilitated Provisions have been made for prolonged care of the subacutely ill especially the rheumatic child (see Table) Custodial care is being instituted for completely and permanently disabled adults Care of a patient with heart disease is a continuous responsibility from onset of his illness to the end of his day

Participating medical agencies are the general hospital hospitals for chronic diseases cardiac clinics sanatoriums and convalescent homes Collaborating nonmedical agencies are public schools vocational training centers certain industrial establishments and voluntary associations consisting of professional and nonprofessional groups interested in the cardiac problem Voluntary groups such as local and national heart associations have been instrumental in formulating plans for collaboration among component agencies and have developed criteria and standards of management for participating institutions

Value of Precordial Lead in Diagnosis of Acute Rheumatic Heart Disease Martin H Wendkos and Kenneth I Zierler (M C A L S) report three cases in which a transient alteration in the T wave of lead CF IV was the only evidence to denote occurrence or persistence of an active myocardial process during the course of acute rheumatic fever Despite this striking T inversion in the precordial lead clinical evidence of structural changes in the heart was not present

Man 23 complained of painful swelling of the right ankle for 24 hours and pain in the right wrist for 12 hours a week after an acute upper respiratory infection this was his first attack of rheumatism He was febrile and acutely ill and an electrocardiogram revealed sinus tachycardia and an inverted T wave in lead CF IV (Fig 7?) Diagnosis was pneumonia and rheumatic fever and sulfadiazine and aspirin were administered Fever subsided the ninth day and joint pains disappeared the sixth day Roentgenograms showed that the pneumonia had resolved without complication or delay On no occasion was there precordial pain or a friction rub Sedimentation rate became normal during the third hospital week rose during the two subsequent weeks before returning again

(1) Cl 3 173 180 J 1944

disease At present it may be concluded that heredity is primarily responsible for the familial incidence the race risk determining the time of occurrence of cases in the family

Community Cardiac Program and Role of the Modern Cardiac Clinic is described by Irving R. Roth[9] (New York City) As a result of evolution of a broad community cardiac program during the past 25 years management of patients with heart diseases has changed radically Diagnosis is now expressed in terms of comprehensive patterns which identify the patient with well

FACILITIES FOR SANATORIAL AND CONVALESCENT CARE OF RHEUMATIC CHILDREN IN NEW YORK CITY AND VICINITY

Institutions	Bed Capacity	Patients As of Jan 1 1942	New Admissions	Readmissions	Census for 1942	Discharges	Patients As of Dec 31 1942	Duration of Stay (Mo) 6 or Less	6 12	12 24	24 [illegible]
A	108	108	78	32	218	109	109	24	53	28	4
B	30	29	34	17	80	50	30	22	20	8	0
C	24	31	34	2	67	46	21	25	11	7	3
D	150	117	160	21	298	147	151	23	97	26	1
Total	312	285	306	72	663	352	311	94	181	69	8

defined clinical categories and treatment is conducted by a group of collaborating agencies The aim is a broad community program with the hospital as the central unit the cardiologist as co ordinator the public as collaborator and the patient as the principal concern

The cardiac child is enabled to acquire an education the adolescent and young adult is being prepared for a suitable vocation Problems arising out of courtship marriage child bearing and infant rearing are receiving consideration Adults of middle age who have suffered an acute cardiac accident or those who have reached the stage of transient breakdown in circulatory efficiency are being

(9) J Mt Sinai H p 10 516 J Feb 1944

barium bolus Even slight posterior deviation of the esophagus is significant and may occur long before the cardiac outline is otherwise altered

In a girl 13 with a history of chorea and migratory joint pains first examination revealed a systolic apical murmur transmitted to the axilla interpreted as due to mitral insufficiency Heart measurements taken from the teleroentgenogram at this time were normal but cardiac fluoroscopy



F g 73 (l ft) —H t lh tt m l d t l g d cco d to
m m t

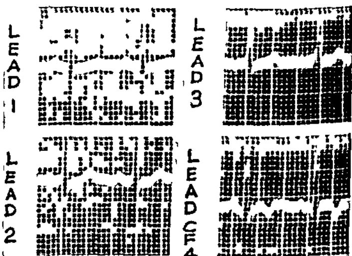
F g 74 (ght) —S m R gh t bl q p j n h g
d t t f l g d l ft l t b m fill d ph g

revealed indentation of an enlarged left auricle into the barium filled esophagus in the right anterior oblique projection (Figs 73 and 74) Three years later systolic and diastolic apical murmurs were present and two years later they were unchanged

Other methods for determining cardiac enlargement based on calculations made from teleroentgenograms and tables of patients heights and weights are unreliable in detecting early left auricular enlargement The frontal silhouette of the heart may retain a normal appearance even when the left auricle is considerably enlarged posteriorly It is necessary to examine patients with systolic apical or transitory murmurs with these facts in mind A diagnosis of a functional murmur should not be made

to the normal level where it remained Electrocardiograms showed P R intervals varying between 0 16 and 0.20 second During the first four hospital days the T wave was flat in lead I and inverted in lead CF IV The fifth hospital day T_4 became diphasic the diphasic character was more definite the sixth day The eleventh day T_4 became upright and subsequent tracings were similarly normal

Until more exact data are available the authors believe



F — El ctr ca d og am on dm ted T w al ng l ad CF IV ta by rdia and

these changes in the precordial lead during acute polyarthritis are related to an acute circumscribed myocardial change not sufficiently extensive or intense to prevent its reversibility

Early Roentgen Recognition of Mitral Valve Disease Bernard S Epstein (Jewish Hosp Brooklyn) state that the earliest enlargement of the heart due to mitral valve disease is left auricular enlargement This can best be diagnosed fluoroscopically by examining the patient in the right anterior oblique projection after administering a

(2) J P di t 23 381 390 Oc obe 1943

must be tactfully guided into occupations in which their livelihood is not dependent on their physical endurance They should be guarded from undue exposure to the weather and should not engage in strenuous competitive sports At the same time the physician must not alarm them unduly They should be carefully followed so that further knowledge may be gained as to prognosis and ultimate outcome of these minimal lesions

National Conference on State Rheumatic Fever Programs is reported by Betty Huse (Children's Bureau Washington D C) Since 1939 a portion of Federal funds appropriated annually for crippled children's services under the Social Security Act has been used for development of rheumatic fever programs Fourteen states have programs in operation and several others have completed plans for them

That rheumatic heart disease is responsible for thousands of rejections from the armed forces was pointed out by Leonard G Rowntree Among 13 000 000 men examined over 230 000 were classified as 4F because of heart disease and Rowntree estimated that nearly half of these defects were caused by rheumatic fever Hugh Morgan reviewed current experience in the Army in dealing with rheumatic fever which indicates that the problem is essentially the same as in civilian practice He urged that civilian health authorities follow the lead of the Army in taking vigorous steps to combat this disease

Use of small daily doses of sulfonamides is remarkably effective in preventing recurrent attacks of rheumatic fever but warning was given against indiscriminate use of sulfonamides without close medical supervision Use of these drugs in prophylaxis should be considered only an adjunct to a regimen of general health supervision for the rheumatic child

Emphasis was placed on importance of early diagnosis during the initial attack referral of patients to special diagnostic clinics examination of siblings of rheumatic

(4) \ s Lett Am H t A \ mbe 1943

if there is roentgen evidence of an enlarged left auricle. Neither should a heart be considered normal if the murmurs are transitory or temporarily absent in the presence of an enlarged left auricle.

Valvular Heart Disease Previously Unrecognized in Military Examinations. Joseph H. Delaney, Samuel I. Miller, Robert W. Kimbro and Louis F. Bishop, Jr.[3] (M.C., A.U.S.) report that approximately two per thousand of a large number of men aged 18–27 were found to have hitherto unrecognized valvular heart disease despite the fact that they had all been given two or more physical examinations. The condition most frequently unrecognized was aortic insufficiency. In almost every case the valvular disease was minimal and was associated with minimal cardiac hypertrophy. That only 35 per cent gave a history of any manifestation of rheumatism is in contrast with the fact that in most series the usual figure is 70 per cent or over.

These findings suggest that there must be a large number of young persons with unrecognized minimal valvular disease in the general population. Importance of early recognition from the military viewpoint is obvious. The group is also important from the industrial, insurance and public health viewpoints. This study shows that many physicians do not recognize these lesions. They are accustomed to think of aortic insufficiency as occurring only with great enlargement of the heart, a loud diastolic murmur, low diastolic blood pressure and classic peripheral signs. That mitral stenosis occurs in the absence of dyspnea on exertion, a loud, easily audible murmur and a large left auricle is not appreciated. These unrecognized patients do not consult the doctor because of symptoms of heart disease but for other reasons, and careful auscultation even in the absence of a history of rheumatism will yield fruitful results in discovery of minimal valvular heart disease.

Once diagnosis is made, management should be skillful so as not to make these patients heart conscious. They

(3) J. A. M. A. 123:884-886 (Dec. 4) 1943.

mately the same The condition is more common in Negroes than in white persons under 40 The high percentage (47 4 per cent) of hypertension in cases of cardiovascular syphilis studied is not purely coincidental but no valid reason is advanced for its presence This study indicates that uncomplicated aortitis is more common in congenital syphilitics than previously believed Of 128 patients with cardiovascular syphilis who remembered their chancre uncomplicated aortitis was diagnosed in 38 within 10 years after the primary infection Neurosyphilis was present in 26 6 per cent of the patients with cardiovascular syphilis

Uncomplicated aortitis is a symptomless disease but can be diagnosed clinically in a normal sized aorta The following criteria are suggested in patients under 40 years (1) A characteristic aortic second sound This may be described as tambour or drumlike tympanitic or hollow and usually is heard over the second and third right sternal space and sometimes over the fourth space (2) Systolic murmur over the aortic area (second third or fourth right sternal space over the sternum the third left sternal space or in more than one of these areas) A systolic murmur has been heard in many instances over the mitral area (3) Suprasternal (episternal) pulsations indicating elongation and dilatation of the aortic arch (4) Increased retromanubrial dulness in the second intercostal space This sign is of value only when the aortitis is far advanced and there is moderate or marked widening of the aorta (5) Hypertension both systolic and diastolic pressures are elevated (6) Corroboration of clinical findings by fluoroscopy and roentgenography to demonstrate presence or absence of a widened area

Patients with cardiovascular syphilis show a greater tendency to react unfavorably to antisyphilitic medication and the reaction is likely to be more severe and dangerous than in a patient without heart involvement Hence treatment of patients with cardiovascular syphilis should be planned with prevention of these reactions in mind Dur

children provisions for institutional care during the period of active infection for educational and recreational activities for children confined to bed for long periods and for schooling for children with heart disease and co ordination of community facilities and services for care and management of the rheumatic child Rheumatic fever represents an important public health problem in the United States but facilities and services have not been developed for adequately meeting needs of children with this disease Local physicians should become more fully acquainted with the disease and with methods for care and management of the rheumatic child Problems of these children cannot be met by services of any single individual or agency but call for close co operation of physicians nurses social workers educators and others engaged in related fields Progress has been made in many states during the past three years through development of state programs and there is need for extension of existing programs and development of similar services in other states

Cardiovascular Syphilis

Cardiovascular Syphilis Its Early Clinical Recognition and Early Treatment The commonest form (70 per cent) of visceral syphilis is syphilitic aortitis yet it is the most frequently overlooked Morris Dressler and Moses Silverman report a study of 1 270 patients with proved syphilis observed in two years at a large social hygiene clinic of the Department of Health New York City undertaken to call attention to the confusion existing regarding diagnosis of uncomplicated syphilitic aortitis and to evolve a method for its early recognition

Of this series 304 (24 per cent) were diagnosed clinically as having uncomplicated aortitis and 390 (30 7 per cent) constituted the entire group with cardiovascular syphilis Of the latter group 78 per cent had uncomplicated *aortitis* The proportion of males to females was approximately 2 1 and that of white to Negroes was approxi

(5) M B ll X t Ad 0 1 35 T 1 1943

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Patients with cardiovascular syphilis show a greater tendency to react unfavorably to antisyphilitic medication and the reaction is likely to be more severe and dangerous than in a patient without heart involvement Hence treatment of patients with cardiovascular syphilis should be planned with prevention of these reactions in mind Dur

ing treatment or immediately thereafter the patient may suddenly become pale with marked tachycardia cold perspiration and failing pulse and occasionally dies in a few minutes This reaction is likely to occur with old arsphenamine and may be due either to greater toxicity of the drug or possibly to the greater volume of fluid necessary for its administration Less toxic drugs and administration in smaller and more easily controlled doses are indicated

All patients with cardiovascular syphilis should be *started with a preparatory course of bismuth and iodides* before any arsenical treatment is attempted Except for patients with uncomplicated syphilitic aortitis the dose should not exceed 0 3 Gm neoarsphenamine or 0 03 Gm mapharsen in any cardiac condition Old arsphenamine should never be used The course should be continuous without any rest period and if there are no reactions or contraindications should be continued at least two years Usually the best procedure is to alternate courses of 10–12 injections of bismuth with 10–12 of arsenicals The serologic report should not alter the length or type of treatment *After two years the patient is given a rest period* of six months if sufficiently improved but is instructed to return for check up and additional treatment if needed

ANATOMIC DIAGNOSIS

THROMBOSIS OF CORONARY ARTERIES

Coronary Heart Disease Angina Pectoris Acute Coronary Insufficiency and Coronary Occlusion A M Master (Natl Naval Med Center Bethesda Md) states that with increasing life span coronary heart disease has taken a pre eminent position since the turn of the century In the 1940 census report there were 385 191 deaths from heart disease a mortality rate of 292 5 per hundred *thousand* the largest ever recorded for heart disease (see

(6) Ann Int Med 0 661 674 Apr 1 1944

Table) Although the high incidence of coronary disease in physicians has been stressed it is ubiquitous and spares neither the sedentary person laborer soldier nor sailor It is the chief cause of death in this country Military personnel more than civilians fail to appreciate the omnipresence of coronary heart disease This disease should be ruled out in all officers and men over 30 by using a test for latent coronary insufficiency such as the electro

cardiogram and the two step exercise (Figs 75 and 76)

The terms angina pectoris due to coronary disease and acute coronary insufficiency are specific and should be retained Their diagnoses are simple to make clinically

DEATHS FROM HEART DISEASE

Age	1940	1900
Under 1	17 5	147.8
1–4	3 6	15 0
5–14	8 0	23 3
15–24	14 0	28.8
25–34	29 7	43 4
35–44	91 7	80.8
45–54	279 5	173.0
55–64	713 5	414 1
65–74	1 723 5	957.3
75 and over	4 813.2	1 819 7

Coronary insufficiency has a characteristic picture and coronary occlusion actually possesses a pathognomonic pathologic and electrocardiographic pattern Angina pec

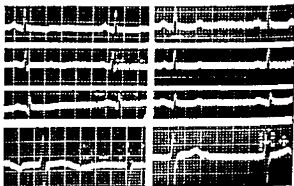
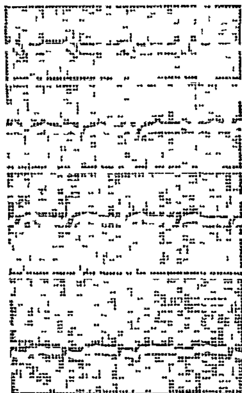


Fig 76—Sam as p ec d g Left July 14 1942 ttack of co y le t d a e w th se e h t p n fo wh h h w ho p t l ed T n ted and T so-electr c R ght July 5 r t n to n rmal traci g

toris due to coronary disease is a transitory attack of anterior chest pain precipitated by exertion emotion cold trauma ingestion of food etc and relieved by nitroglycerin It is due to temporary ischemia and is not accompanied by pathologic change in the myocardium

Acute coronary insufficiency is usually ass ed with

a precipitating factor such as causes an ordinary attack of angina but also is observed in tachycardia heart failure acute hemorrhage operation shock aortic stenosis and insufficiency syphilitic coronary ostitis etc which reduce



F g 77 —M 57 w th hypert d ry h t d se w th t ta ks f *er* h t *pa n. A top y* al d l g l ft t *cle my dial* sc ng and ever scl b t n l f co ry ter Elect d g am (N mber 20) h w d p f RS T ll l d m t d so lect T d t d T V d g tal

coronary flow or increase the work of the heart and oxygen requirement of the heart muscle If ischemia is severe and prolonged focal disseminated necrosis in the subendocar

dium and bases of the papillary muscles will result Depression of the RS T segment and T wave inversions are characteristic (Figs 77 and 78)

Coronary occlusion or thrombosis occurs irrespective of

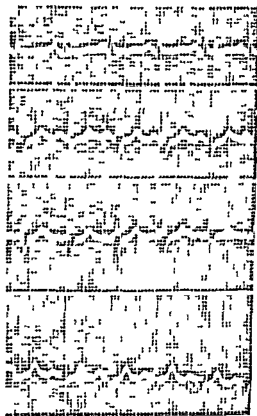


Fig 8—S m se p ec d g Decembe 1

external factors except possibly operation and shock Shock nausea and vomiting a fall in blood pressure distant heart sounds left heart failure fever leukocytosis and rapid sedimentation rate are practically always found Gallop rhythm and pericardial rub may be heard P thologic and

electrocardiographic findings are specific A confluent massive infarct extends from endocardium to pericardium thus frequently giving rise to embolism and pericarditis The electrocardiogram discloses RS T elevations (which progress into T wave inversion) deep Q waves and a reciprocal relationship of the RS T and T wave changes in leads I and III

Controversial Issue of Use of Digitalis in Coronary Arterial Disease Fredrick A Willius (Mayo Clinic) states that presence of congestive heart failure or evidence of its imminent supervention constitutes the chief indication for digitalis therapy in coronary arterial disease The drug must be administered cautiously because patients with this cardiopathy tolerate digitalis less than those with other forms of heart disease Unless onset of failure is precipitous and severe it seems justifiable to resort to complete rest and use of mercurial diuretics before using digitalis If cardiac function has been restored to permit a restricted ambulatory mode of life regular intermittent administration of digitalis for protracted periods is commendable However its use should always be cautious the drug should be administered only under strict supervision so that any signs of intolerance may be readily detected

Contraindications to digitalis therapy are (1) anginal syndrome of coronary disease without previous or existent congestive heart failure (toxic doses and sometimes even average doses of digitalis may cause painful seizure to occur more frequently and with less provocation) (2) coronary occlusion with acute infarction of the myocardium unaccompanied by congestive heart failure (3) healed infarction without previous or existent congestive heart failure (4) coronary sclerosis with impairment of ventricular conduction (delayed AV conduction complete heart block and bundle branch block) without previous or existent congestive heart failure (5) mere suspicion of coronary disease (often based on presence of pain in the left side of the thorax)

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Coronary Disease Recognition and Management are discussed by Harry L Smith[8] (Mayo Clinic) Coronary sclero is associated with angina pectoris must be distinguished from pain in the wall of the thorax intercostal *neuralgia myositis arthritis of the spinal column* spasm or diverticulum of the esophagus cardiospasm diaphragmatic hernia duodenal or gastric ulcer gallbladder disease functional indigestion scalenus anticus syndrome radicular pain and acute coronary occlusion also from cardiac neurosis bronchial asthma associated with bronchitis and emphysema Dyspnea is an important symptom of heart disease but in mild or moderate angina pectoris pain often may limit the patient s activity and thus prevent occurrence of dyspnea In most cases of coronary disease however dyspnea is more severe than before the disease developed In severe cases dyspnea is an important symptom A normal electrocardiogram does not rule out coronary disease In atypical cases the anoxemic test is of considerable value Ten per cent oxygen is administered for 20 minutes if coronary disease is present a change will occur in the S T segment or the T wave will be inverted If substernal pain and dyspnea should develop during the test 100 per cent oxygen should be administered immediately Site and extension of *pain in coronary occlusion* are the same as in angina pectoris but the pain is much more severe and of much longer duration In acute coronary occlusion clinical signs of shock usually are present Blood pressure generally falls pulse may become weak and *thready and temperature may increase to 100 or 102 F* Leukocytosis develops after a few hours and sedimentation rate rises A friction rub may be heard if the infarction involves the anterior surface of the left ventricle In acute coronary occlusion electrocardiography is more important *in establishing the diagnosis than in other types of heart* disease

Treatment of mild coronary sclerosis consist mainly in instructing patients to slow up in their work They should

(8) J Iowa M Soc 33 543 546 D be 1943

be advised to work less strenuously and under less emotional and nervous strain and to obtain more sleep They should avoid eating large meals and should rest 30 minutes to 1 hour after eating If overweight they should reduce They should avoid any activity which induces pain Patients with severe coronary disease and angina pectoris should receive similar advice but should follow a much more rigid program Glyceryl trinitrate should be administered to relieve pain It is sometimes advisable to give 1½ gr of aminophylline three times daily If patients are nervous and do not sleep properly they should receive small doses of phenobarbital or seconal Often it becomes necessary to place patients at complete rest for 10 days to 2 weeks and books and other diversion should be furnished for relaxation Patients sometime have to reduce their work change their vocation or discontinue work entirely In many instances acute coronary thrombosis will develop later

In acute coronary occlusion pain must be controlled and complete rest secured Pain is best controlled by morphine doses of ½ gr may be required Amyl nitrite and glyceryl trinitrate are not indicated as they tend to lower blood pressure which is already decreased Digitalis is not administered unless symptoms of heart failure gallop rhythm or auricular fibrillation is present Although some physicians administer quinidine in all cases Smith believes it should be used only if frequent extrasystoles occur Oxygen is given for pain dyspnea cyanosis and restlessness either in a tent or with a mask Patients should be kept in bed three to six weeks depending on severity of the attack and the age Very old patients are not kept in bed too long often they are allowed to sit up in a chair one week after acute occlusion All patients are allowed to use a commode at the side of the bed instead of the bedpan Smith believes with skilled assistance of nurse and orderly that there is less strain with the former than with the latter Death has occurred during use of a bedpan but he knows of none during use of a commode

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likely not to be disclosed by electrocardiographic examination than is involvement of the posterior wall

Electrocardiographic diagnosis and location of the infarction are highly accurate Correlation of autopsy and electrocardiographic material revealed 16 cases in which the electrocardiogram did not correctly localize the infarct In eight only one electrocardiogram was taken before death in two bundle branch block was present and in two a diagnosis of acute infarction of uncertain origin was made Therefore these should not be considered as instances of electrocardiographic error Of the remaining cases there were three in which anteroposterior infarction was partially but not completely diagnosed In just one case (interpreted as one of posterior infarction and found to be one of anterior infarction) was there a definite diagnostic error

Treatment of Coronary Thrombosis N C Gilbert (Northwestern Univ) states that treatment must be immediate *Even if diagnosis is uncertain it is better to treat* a patient for coronary occlusion even though an occlusion has not actually occurred than not to treat him for coronary occlusion Gilbert uses atropine routinely in all cases in which the occlusion is at all recent Its beneficial action is due to abolition of reflex vasoconstriction as has been shown experimentally It is given subcutaneously in doses of 1 100 or 1/75 gr The dose is repeated in four to eight hours as indicated and is discontinued as soon as conditions appear stabilized which may be after the first dose or not until 24 or 48 hours have elapsed More than three doses of atropine are rarely required

Also in keeping with the rationale of reducing or minimizing the area of infarction is use of coronary vasodilator drugs In this regard both experimental and clinical observations indicate the value of drugs of the purine series Among these is aminophylline which may be used intravenously or intramuscularly For intravenous administration the 10 or 20 cc ampule containing 3¾ or 7½ gr 1

(1) M Clin N th Am 8 1 15 J 1944

Prognosis depends on size of the infarction whether or no canalization occurs or an adequate collateral circulation develops and general condition Not so many patients die in the original attack as was once thought now it is believed only 30–50 per cent succumb at this time In some cases the heart is so severely damaged that it is incapable of continuing its work In a fair number proper treatment and care will permit patients to recover and continue a rather active and useful life for many years after they have suffered an attack

Acute Myocardial Infarction Diagnosis and Location of Infarct by Electrocardiogram Samuel Baer and Harold Frankel (Jewish Hosp Philadelphia) considered the diagnosis and location in 378 cases Electrocardiograms made in 321 cases revealed infarction in 94 per cent In 13 of the 18 cases in which myocardial infarction was not diagnosed only one electrocardiogram was taken and in 5 cases a diagnosis of bundle branch block was made The authors agree with Barnes that repeated electrocardiograms should reveal infarction in practically every case

On electrocardiographic study alone 52 per cent of the infarcts were anterior and 34 per cent posterior (see Table) In 74 cases seen at autopsy 70 per cent of in-

LOCATION OF ACUTE INFARCTION BY ELECTROCARDIOGRAM

	Cases		Deaths	
	No	%	No	%
Anterior	167	52	47	28
Posterior	108	34	22	20
Anteroposterior	7	2	2	28
Acute infarction, location uncertain	21	7	6	28
Electrocardiogram not diagnostic	13	4	9	69
Bundle branch block	5	1	5	100
Totals	321	100	91	28

farcts were anterior 23 per cent posterior and 7 per cent anteroposterior Anterior myocardial infarction are more frequent and more serious than posterior infarction Infarction of the anterior wall of the left ventricle is more

(9) Arch Int Med 73 86 87 Apr 1944

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(1) M Cl N th Am 8 1 15 T 1944

used the solution being injected very slowly Intravenous administration has the advantage of more rapid action and avoidance of the painful area which is apt to follow intra muscular use a disadvantage is that a fall in blood pres sure may follow especially if injection is too rapid For intramuscular use the aforementioned dosages are pre pared in 2 cc ampules

Papaverine hydrochloride is a coronary vasodilator of equal value with aminophylline It has little or no hypnotic effect It can be given intravenously or hypodermically in doses of ½–1½ gr For intravenous use 1 gr should be sufficient

Morphine pantopon or another narcotic should be given for pain but must always be given with at least 1/100 gr atropine Oxygen should be given immediately prefer ably through an oxygen tent Oxygen should be continued for one or two days or longer until pulse and respiration are approximately normal and cyanosis is improved When the immediate emergency has passed the purine drugs or papaverine may be given orally Morphine is best not used after it has relieved the initial pain

[Many excellent cardiologists believe that quinidine sulfate should be used immediately and continuously following a coronary throm bosis—with or without the presence of premature contractions—in the hope of lessening myocardial irritability and thus preventing the onset of ventricular fibrillation and sudden death —Ed]

Lateral Coronary Syndrome, a new clinical entity is described by Guillermo A Bosco[2] on the basis of his con cept of myocardial ischemia derived from anatomic pathologic and clinical study He considers the way the coronary arterial system irrigates the heart the two dis tinct types of distribution of the left circumflex artery delimitation of myocardial areas subsidiary to this and the other two coronary branches (descending anterior and right circumflex) the anatomicohistologic structure normal and pathologic of cellular systems forming these areas and other cardiac compartments chronology of

(2) S nd om s Arte C xar s S p m Co a o L t (B n s A Imp t Fe a H 1943)

changes of the left coronary branches and physiologic and pathologic phenomena in the heart and aortic arterial tree during the cardiac cycle in normal subjects and in those with myocardial ischemia

Bosco shows that myocardial ischemia is routinely a localized process in the left ventricular area because the descending anterior and left circumflex arteries of normal or anomalous distribution are affected early and always before the right circumflex artery and because the obstructive process develops with greater rapidity in the left portion of the coronary system since it is predisposed to change by anatomicofunctional factors in the left ventricle Consequently ischemia of the myocardium is a process of elective localization in this cardiac compartment

The lateral coronary syndrome is originated habitually by an occlusive arterial process which is situated rarely in the full body segment of the left circumflex artery but usually in its terminal portion or in some of its collateral branches preventricular lateroventricular or retroventricular Obstruction of the left circumflex artery is the most common pathologic finding in the coronary arteries this localization was found in 70 per cent of Bosco s cases of myocardial ischemia Localization in the posterior wall of the left ventricle is of the same frequency because that is the site of termination of the left circumflex artery of normal type distribution (80 per cent) while the left circumflex artery of anomalous type enter the posterior wall of the right ventricle in the remaining 20 per cent

Obstruction of the left circumflex artery of normal distribution is definitely responsible for production of ischemia in the lateral wall of the left ventricle and this is the basis of the lateral coronary syndrome Localization in the main segment in the terminal portion or in collateral branches of the artery of normal distribution conditions the magnitude of myocardial damage If the main segment is obstructed ischemia of the lateral wall of the left ventricle will be considerable in which case the manifestations of the coronary lateral syndrome are complete indicating that

the picture of acute myocardial insufficiency is grave If on the other hand the obstruction is in the terminal portion of the vessel or one of its collateral branches the degree of ischemia is reduced and the resulting myocardial insufficiency is benign

It is important to recognize that when the left circumflex artery is of anomalous type distribution it supplies in 20 per cent of cases the interventricular wall and the posterior wall of the right ventricle In such case the ischemia is found in this situation which permits the conclusion that ischemia of the right ventricle is not a definite anatomicoclinical reality but is complementary since myocardial ischemia is pre eminently a process involving the left ventricle

The cardiac muscular system is not the only one suffering effects of the anemia produced by coronary obstruction Other cellular systems ensorimotor endocardial and pericardial participate al o in changes produced by insufficient circulation and their anatomic and functional disorders are indicated by definite and specific symptoms Such is the origin of paroxysmal tachycardia due to extrasystoles of the left ventricle and of pericardial rubs systolic murmurs and other symptoms

Exact appreciation of all these clinical symptoms and their correct diagnostic value is possible with application of this concept of disorder of the coronary arterial system

Surgical Procedures in Cases of Healed or Healing Myocardial Infarcts present two basic problems according to F A Willius These are the imperative nature of the surgical condition and the status of the heart and its probable re ponse to the contemplated operation An imperative surgical condition is of decisive importance and constitutes a significant complication in a medical problem The complicating disease must be so important that the patient s life is threatened if operation is not performed Among these complications are carcinoma prostatic ob struction obstructive perforative or hemorrhagic peptic

(3) Proc Staff Meet Mayo Clin 18 374 376 Oct. 1943

ulcer acute gangrenous cholecystitis obstruction of the common bile duct acute gangrenous appendicitis intestinal obstruction and strangulated hernia These conditions present serious problems even when the heart is normal When it is still undergoing repair after acute myocardial infarction the surgical hazards are greatly amplified

Numerous factors relating to the heart itself must be carefully appraised The time since abrupt closure of the coronary artery is of prime importance Even when the clinical course progresses satisfactorily the infarct is not converted into a well condensed cicatrix in less than three months and by that time repair is not complete because *production of collateral circulation has really just begun* Months and even years are often required before vascular adequacy of the heart is restored to the point of functioning *without symptoms* and sometimes this is never achieved The anginal syndrome is unmistakable evidence of coronary insufficiency and indicates that vascular anastomoses are not sufficiently developed for performance of cardiac function Marked heart damage is revealed by enlargement congestive failure and disturbances in conduction Cases in which the interventricular septum has been involved in infarction are potentially serious despite immediate survival Marked hypertension adds significance to the problem because addition of this increased load to an already damaged heart favors progression of hypertrophy and dilatation and ultimate congestive heart failure

Whenever possible a year should elapse before the patient with a healed cardiac infarct is subjected to operation When the complicating condition does not permit procrastination choice must be made between accepting the added risk of operation (with everyone concerned understanding the fact) and accepting death from the complicating disease by not operating This latter decision usually is not made by either surgeon or clinician because experience has shown that the cardiac mortality rate even under these uncompromising conditions is not prohibitive

However this decision may be made by the patient or the relatives and it is important that the physician emphasize that if the chance of surgical intervention is rejected no regrets should be manifested later

Operative risk is grave when only a short time ha elapsed since coronary closure Hence the scope of the procedure should not be extended beyond that absolutely necessary the operation time should be as short as possible and choice of anesthesia should take into full account the cardiac as well as the surgical problem Postoperative management also must be wisely considered and such procedures as oxygen therapy blood or plasma transfusions and parenteral administration of other fluids cautiously individualized Excessive administration of fluid to a patient with a failing myocardium is inadvisable

Little is to be gained by preoperative cardiac treatment excepting in case of congestive heart failure in which operation can only rarely be considered and then only after cardiac function has been reasonably restored Patients with healed or healing myocardial infarcts who exhibit congestive heart failure are almost always in desperate condition They may be grouped into those with (1) marked cardiac enlargement with or without ventricular aneurysm (2) multiple infarcts (3) severe hypertension and (4) associated and independent cardiac lesions

Prothrombin Determinations in Acute Coronary Occlusions Observations by H McGuire Doles (Norfolk Va) suggest that vitamin K deficiency is a factor in the mechanism of acute coronary occlusion Prothrombin determinations were made on 457 persons over half of whom were patients with varying degrees of hypertension In 8 of the 457 acute coronary occlusion developed during observation 5 were not seen until after occlusion occurred Figure 79 shows the prothrombin levels observed in these individuals

Analysis of the prothrombin determinations in this group is rather significant Of the eight in whom acute coronary

(4) S th M J 6 09 13 N be 1943

occlusion developed the occlusion did not occur until prothrombin time was below 70 per cent of normal Accordingly orthodox treatment of acute coronary occlusion was supplemented by use of vitamin K given parenterally initially and orally subsequently In the patients in whom

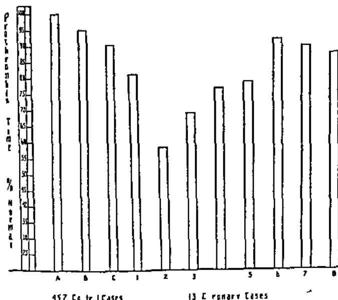


Fig 79—*A* mal s bj t *B* p t t wh ll w t l ted to d l j t m *C* pat t w th hyp t 1 o ry case bef 1 2 1 48 h ft l on 3 72 hou 4 th d y 5 f rst th d y 6 th w k 7 t lfth m th 8 tw ty f th m th

the prothrombin time was restored to normal limits shortly after acute onset convalescence was less stormy and the amount of myocardial damage resulting from the occlusion appeared to be considerably less

Disabling Changes in Hands Resembling Sclerodactylia Following Myocardial Infarction Disabling trophic changes and deformities of the hands and fingers resulting from local ischemia are well recognized sequelae of

However this decision may be made by the patient or the relatives and it is important that the physician emphasize that if the chance of surgical intervention is rejected no regrets should be manifested later

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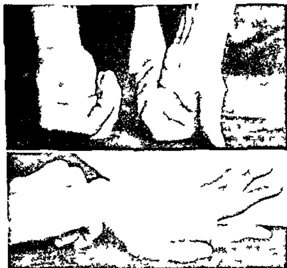
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(4) South M J 36 09 13 November 1943

neither complete flexion nor extension could be accomplished (Figs 80 and 81) Soft tissues over phalanges on the dorsal surfaces appeared to become more tightly attached to the underlying structures Soft tissue atrophy made the metacarpals stand out and the tendons became more prominent Contractures of the palmar fascia were not as apparent at this stage as later in the course of the disease In some long standing cases roentgenograms



F g 80 (t p) —M m m p bl fl f fi g
F g 81 (bott m) —S m S [] t lt g f m l t ffo t
t h f ll en f fi g ff n f f sm ll g f
t t d n l d t f w t Sk pt tightly rl d t
jh l g d t ph d b d b k f b d

showed disuse atrophy of the bone These characteristics of the hands and fingers were constant in the later stage in all cases although variable in degree in individual patients

Johnson suggests that the etiology of postinfarction sclerodactylia is anoxia of the tissues of the fingers produced chiefly by ischemia resulting from reflex vasocon

external vasoconstriction from the splinting of injured hands and of intrinsic vasoconstriction from overactivity of the sympathetic nervous system Scleroderma and sclerodactylia develop in Raynaud s disease Similar trophic changes in the hands occurring as a sequel of acute myo cardial infarction in 39 of 178 consecutive cases of myo cardial infarction are reported by Alf C Johnson[5] (Great Falls Mont)

The first symptoms which attracted the patients atten tion and which appeared 3–16 weeks after the acute myo-cardial infarction in this series were pain and stiffness of the fingers Uniform firm bilateral symmetrical swelling of the entire hands including the fingers appeared The swelling did not pit on pressure The skin became smooth and tight and normal skin wrinkles were more shallow or were entirely obliterated especially the transverse wrin kles over the backs of the fingers Color changes in the hands occurred varying from erythema to different grades of cyanosis The hands and fingers were cold to touch and no consistent moistness dryness or sensory changes were noted No striking changes were present in volume of the pulse in the radial or brachial arteries although these vessels usually were thickened and sclerotic The fingers could never be fully extended or flexed and manipulation caused pain on increased motion Effusion in the joints and crepitation never developed No nodules or nodes were observed except in patients with pre existing hypertrophic arthritis These characteristics were noted in the early stages in all cases

With passage of time and regardless of therapy swell ing of the fingers and hands subsided but no particular changes occurred in the pain or stiffness of the fingers The skin which at first appeared thin and glossy now became thickened and dull in color sometimes bronzed Joints and bony prominences were more apparent because of shrinkage of the soft tissues over the phalangeal shafts Movements of the fingers were limited and painful and

(5) A n I t M d 19 433 456 S ptembe 1943

angina of effort brought the over all average survival close to that of the larger group Gross myocardial infarc tion recognizable clinically followed angina pectoris decu bitus within 24 hours in 22 cases and within 3 months in 19

An important by product of this study is confirmation of the suspicion that coronary heart disease whether shown by angina pectoris or temporary coronary insuffi ciency or by myocardial infarction with subsequent scar ring is actually usually an acute or subacute rather than a chronic disease though frequently it recurs Coronary artery damage may be permanent and therefore chronic but its effect on the heart itself is the important point thus coronary disease and coronary heart disease must be *clearly differentiated This conception of the frequent* acuteness or subacuteness of coronary insufficiency is of tremendous significance in both prognosis and treatment Special care during acute and subacute phases of coronary heart disease replacing the old fatalistic viewpoint is the most important part of treatment and is sometimes ignored in the course of introduction of new therapeutic measures

Paroxysmal Cardiac Pain Differential Diagnosis and Treatment of "Angina Pectoris' Harold L Rakov sug gests substitution of the term paroxysmal cardiac pain with appropriate qualification for angina pectoris which to the laity presages impending terrifying death Paroxys mal pseudocardiac pain around the precordium is not associated with disturbance of coronary circulation or actual coronary disease a common form is pain arising from osteo arthritis of the cervical spine Paroxysmal benign cardiac pain arises in the heart from qualitative or quantitative disturbance of coronary circulation Patho logically there is no significant evidence of coronary arterial disease Paroxysmal malignant cardiac pain around the precordium is caused by disease of the coronary arteries which produces cardiac ischemia

Clinical manifestations of coronary artery sclerosis seem

(7) U S N M B ll 4 116 3 4 F b y 1944

striction of the arteries of the hand induced by cardiac pain and that the lesser ischemic effects of arteriosclerosis of these arteries and the local anoxemia of the fingers which is part of the general anoxemia resulting from myocardial injury may increase the degree of the damaging tissue anoxia

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PHYSIOLOGIC DIAGNOSIS

Anginal Syndrome

Prognosis of Angina Pectoris A long time follow up of 497 cases first observed between 1920 and 1930 is reported by Paul D White Edward F Bland (Boston) and Edward W Miskall[6] (East Liverpool O) with a note on 75 additional cases of angina pectoris decubitus Of the 497 *patients with angina pectoris 445 are dead Average survival to death was 7 9 years while average survival from* onset in the 52 living is 18 4 years average for the total series 9 years will increase before all present survivors succumb Cardiac conditions caused 76 per cent of the deaths Approximately one fifth of the entire group had normal heart blood pressure and electrocardiograms at the first examination and these as a rule lived longer Hypertension myocardial infarction cardiac enlargement abnormal heart sounds congestive failure and abnormal electrocardiogram occurred much more frequently in the group *that died within 3 years than in those living 14* years or more A pronounced degree of nervous sensibility was a favorable influence

Angina pectoris decubitus was found in 103 of the 497 patients there was no significant difference between average survival figures for this group and those for the group as a whole In 75 additional cases of angina pectoris decubitus survival was relatively short after onset of decubitus type of pain averaging 2 8 years in 47 cases followed to death However average duration of precedent

(6) J A M A 1 3 801 804 Nov 27 1943

hould be administered parenterally Digitalis and epineph rine are contraindicated Intravenous administration of some xanthine preparation preferably theophylline ethyl enediamine seems to increase coronary flow but rela tively large doses are necessary and the effect is transient

Present therapeutic measures are often valueless in abating a progressive degenerative vascular process and prognosis varies greatly in different cases Failure to rec ognize the influence of psychogenic disturbances con tributes to therapeutic failure The patient must be told how to avoid attacks and must be reassured Importance of human relationships must not be lightly regarded The organic disease cannot be cured but the physician can mold the patient s outlook and activity to attain some adjustment and harmony

Treatment of Angina Pectoris Summary of 10 Years' Objective Study is reported by Joseph E F Riseman The value of any form of treatment can be determined objectively by measuring the amount of work that can be done before angina is induced provided measurements are made under conditions closely simulating those re sponsible for most of the attacks in daily life and are standardized so that response to therapy is the only variable factor that can influence exercise tolerance

In the standardized exercise tolerance test several often overlooked factors are important (Fig 82) Importance of exercise in the cold must be emphasized for if patients exercise at ordinary room temperatures approximately one third fail to develop an attack whereas in others exer cise tolerance varies independently of therapy If the tests are carried out under standard conditions of low tem perature (45–55 F) one hour after a light meal and if there has been no recent attack and no medication and the patient is familiar with the test the amount of work *necessary to induce angina becomes remarkably constant* (usually around 10 per cent of the average exercise toler ance) [It seems to me that the anoxemia test of Levy

(8) N w E gl d J M d 2 9 670 680 Oct 28 1943

to follow four distinct patterns (1) typical pain (2) gastro intestinal (3) respiratory and (4) atypical The main characteristic of pain of coronary arteriosclerosis is its direct relationship to effort or emotional strain Walking lifting or excitement produces a sensation in the chest or arms that compels arrest of activity After a few moments of rest the distress is gone The pain usually is behind the middle or lower sternum it may radiate down the left or right arm both arms into the back or up into the jaws It is usually described as a viselike sensation Symptoms sometimes simulate those of gallbladder disease or duodenal ulcer with complaint of a vague nauseating distress in the upper abdomen and a desire to belch With the respiratory symptom complex the patient complains of dyspnea on exertion with no pain or paroxysmal nocturnal dyspnea The atypical group usually noted in older patients may be characterized by fainting attacks with pallor great restlessness with sweating or congestive heart failure but no pain About 20 per cent of patients with coronary arteriosclerosis reveal no objective clinical abnormalities Symptoms of acute sudden closure are dramatic Occurrence of temporary hyperglycemia and glycosuria following coronary thrombosis is a physiologic response Administration of insulin in these cases may result in death

Coronary artery thrombosis with occlusion need not lead to myocardial infarction Effective collateral circulation may develop promptly provided there is no excessive cardiac strain Anticipatory treatment will not forestall the threatened occlusion but may diminish the area or intensity of myocardial ischemia Control of pain is of vital importance to prevent reflex spasm of collateral coronary branches Spasmalgin lacks toxic morphine effects and apparently produces beneficial clinical results as does intravenous and oral administration of large doses of papaverine. Oxygen in high concentrations should be administered immediately even when respiratory embarrassment is not present Caffeine sodium benzoate

diminution but not complete disappearance of these attacks An increase of 20 per cent or less usually is unassociated with clinical improvement

The converse is not true since most patients with angina pectoris feel better after visiting the physician regardless of treatment prescribed Furthermore some with infrequent attacks have periods of relative comfort Without an objective test neither patient nor physician can say whether these periods of relief are the specific result of treatment or merely coincidental

Objective study with 68 different treatment methods at a special clinic at Beth Israel Hospital Boston since 1933 showed that 27 per cent (group 1) of a series of patients with angina pectoris responded strikingly to practically all methods of therapy 33 per cent (group 2) responded to a moderate degree and 40 per cent (group 3) usually failed to respond appreciably This variation in therapeutic response should be considered in any study of efficacy of treatment of angina Clinical evaluation of efficacy of therapy is extremely difficult and unreliable Nothing short of complete or almost complete disappearance of attacks can be considered as a favorable response and such periods may be spontaneous and not related to treatment

Of the 68 methods of treatment evaluated 20 were found to be of considerable value 22 of slight value and 26 of psychologic value only In prescribing medicinal therapy the drugs of choice are nitroglycerin (1/400 gr every hour) theobromine and sodium acetate (7 1/2 gr four times daily) quinidine sulfate (3-5 gr four times daily) atropine sulfate (1 150 gr four times daily) enteric coated potassium iodide (1 Gm four times daily) cobra venom intramuscularly and sedatives Treatment was of value in approximately 80 per cent of all the patients About 20 per cent (two thirds of whom were in group 3) responded to none of these medications

Surgery should be considered only if medical measures fail It was performed in approximately 7 per cent of pa

can be better controlled than this exercise tolerance test.—Ed] Several months of observation are necessary to determine usual frequency of attacks in daily life and usual exercise tolerance When these are ascertained medication is given three to four times daily for at least a week. If there seems to be a therapeutic response the psychic factor is eliminated by giving a placebo resembling the drug and later by administering it in disguised form. Electrocardio-

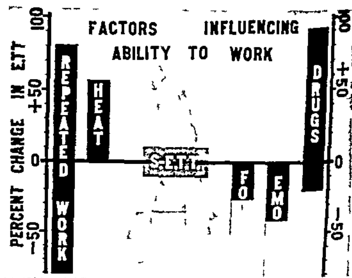


Fig 82

graphic studies give further objective evidence as to response to therapy

This standardized exercise tolerance test makes it possible to differentiate real improvement due to treatment and apparent improvement unrelated to it Patients who show an increase in exercise tolerance of 100 per cent or more following treatment usually have complete or almost complete freedom from attacks in daily life An increase of 30–75 per cent is usually associated with a moderate

diminution but not complete disappearance of these attacks An increase of 20 per cent or less usually is unassociated with clinical improvement

The converse is not true since most patients with angina pectoris feel better after visiting the physician regardless of treatment prescribed Furthermore some with infrequent attacks have periods of relative comfort Without an objective test neither patient nor physician can say whether these periods of relief are the specific result of treatment or merely coincidental

Objective study with 68 different treatment methods at a special clinic at Beth Israel Hospital Boston since 1933 showed that 27 per cent (group 1) of a series of *patients with* angina pectoris *responded strikingly* to practically all methods of therapy 33 per cent (group 2) responded to a moderate degree and 40 per cent (group 3) usually failed to respond appreciably This variation in therapeutic response should be considered in any study of efficacy of treatment of angina Clinical evaluation of efficacy of therapy is extremely difficult and unreliable Nothing short of complete or almost complete disappearance of attacks can be considered as a favorable response and such periods may be spontaneous and not related to treatment

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tients in this series Total thyroidectomy is of considerable value in selected cases Paravertebral injection of alcohol gives symptomatic relief in others

Treatment of Angina Pectoris and Peripheral Vascular Disease with Sex Hormones G F Strong and A W Wallace (Vancouver) administered testosterone propionate or estradiol dipropionate to 20 patients with angina and 4 with peripheral vascular disease Anginal patients were chosen who had typical pain on effort relieved by rest and nitroglycerin and other signs suggesting arteriosclerotic origin All had suffered from angina for several months to several years and knew the relief obtained from nitroglycerin To evaluate results patients were asked to keep a day by day record of attacks and amount of nitroglycerin necessary for control All were started on a series of 12 injections given every four or five days some received a few more and some a few less For the men each injection contained 25 mg testosterone propionate for the women the dose of estradiol dipropionate was 5 mg During and after treatment patients returned for regular check ups The patients with peripheral vascular disease all had severe intermittent claudication and diminished or absent pulsations in the dorsalis pedis arteries Evaluation of treatment was based on subjective improvement and dorsalis pedis pulsation

Seventeen of the 20 patients with angina showed some improvement in 6 this was fairly marked and has lasted from three months to one year the others showed slight to moderate improvement that did not last long after treatments stopped One of the four patients with peripheral vascular disease claimed fairly marked improvement two one of whom also was receiving pavaex treatment claimed slight improvement There was no improvement in the fourth case Objectively there was no definite change in pulsation in dorsalis pedis arteries in any of these patients

The mechanism of these effects must involve both the endocrine and the nervous system in a way that allows

(9) C d M A J 50 30 33 J ua y 1944

increased coronary flow either by vasodilatation or prevention of vasospasm Although the mechanism is not clearly understood it appears from this and other reports that sex hormones are at least of some value in treatment of angina and probably also of peripheral vascular disease Considerable study is required to determine mode of action and specific indications

Therapeutic Value of Testosterone Propionate in Angina Pectoris is discussed by Samuel A Levine and William B Likoff[1] (Harvard Univ) on the basis of a study of 19 cases Testosterone is administered with the hope of improving cardiac blood supply by increasing collateral circulation or degree of vasodilatation of the coronary arteries or both and previous reports of its use have been uniformly favorable The authors used doses of 25 mg three times a week for four weeks in 18 patients and for seven weeks in 1 patient All but two patients received no other medication and continued their accustomed daily routine Of the 19 patients 9 had hypertension and 1 rheumatic aortic stenosis and insufficiency Five had had a previous coronary occlusion Results were judged by amount of physical activity necessary to produce an anginal attack and number of nitroglycerin tablets used daily Degree of improvement was classified a marked moderate and questionable

Five patients were markedly improved at the end of treatment Two however reverted to their former clinical state in six to eight weeks one obtained no relief from a second series of injections after 15 months of comparative comfort and one was followed for only one month One patient was moderately and 2 questionably improved and the remaining 11 obtained no benefit No changes in blood pressure or electrocardiogram were observed and no toxic effects or significant changes in libido were noted The behavior of this entire group was not unlike what would be expected in following any average series of cases of angina pectoris over a short period one patient having

(1) New Engl d J Med. 9 7 0 7 N 18 1943

died unexpectedly and acute coronary thrombosis having developed in another patient in the group

Realizing that the clinical course of angina pectoris may vary a great deal spontaneously the authors are unable to conclude that testosterone propionate has any beneficial therapeutic effect

[These conclusions seem more logical to me than those of the authors of the preceding article —Ed.]

Cardiovascular Dynamics in Patients with Angina Pectoris Mark D Altschule[3] (Harvard Univ) studied the circulation of 22 patients with a history of angina pectoris but without signs or symptoms of congestive failure cardiac arrhythmia or valvular disease Cardiac output and circulation time were normal in relation to metabolic requirements When slowing of the circulation occurred it was due to noncardiac factors Venous pressure was normal in all instances The only common abnormality of cardiovascular dynamics was arterial hypertension

Altschule concludes that a valid generalization based on physiologic data is reaffirmation of the clinical concept that factors which increase cardiac work or decrease myocardial oxygenation lead to angina in patients with disease of the coronary arteries or their ostia although reflex mechanisms are also important in many patients

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ELECTROCARDIOGRAPHY

Normal Variations of T Wave Seen among Soldiers Homer Dupuy (M C A U S) found electrocardiographic changes commonly regarded as indicative of myocardial disease in five young soldiers without clinical or other laboratory evidence of such disease In four cases reversibility of T waves was demonstrated unrelated to an organic lesion in one case the changes probably were attributable to a physiologic factor

(2) Am. Heart J 7 3 330 M h 1944
(3) N w O l a s M. & S J 96 239 247 December

The following factors are important in evaluation of T wave changes (1) character of the waves—the minus plus form particularly when the downward portion is shallow is less significant than plus minus types and may occasionally be seen in any limb lead with an apparently normal heart (2) consistency of changes—waves varying in direction and amplitude in successive cycles of the same lead are less significant than fixed changes (3) rotation of the heart—change of body position inspiration expiration and less frequently deformity of the thoracic cage can affect the T wave (4) anxiety and rapid heart rate—diphasic or inverted T waves with rapid heart rates may become upright with relaxation or sedation and subsequent slowing of heart rate (5) serial tracings—diphasic to inverted T waves in leads I IV on routine tracings may become upright on tracings repeated the following day for no apparent reason i e in absence of history or physical findings suggestive of cardiovascular disease (6) clinical picture (7) consideration of extra cardiac conditions that may produce reversible heart disease e g endocrinopathies avitaminosis blood dyscrasias acute toxic processes drugs or pulmonary conditions causing abnormal cardiac rotation

Dupuy emphasizes that T wave changes suggestive of myocardial disease particularly in the young may result from normal physiologic variations rather than organic lesions Various procedures to determine reversibility of T wave inversions should be carried out routinely

Heart Block Study of 100 Cases with Prolonged P R Interval is reported by Robert Bruce Logue and James Fletcher Hanson (Lawson Gen l Hosp Atlanta Ga) These were found in 6 732 electrocardiograms of 4 264 patients P R intervals of 0 22 second or above occurred in all these cases The high incidence of block in patients with no evidence of heart disease (19) suggests that a prolonged P R interval may sometimes be found without apparent cause While it is impossible to eliminate past

(4) Am J M Sc 207 765 769 J 1944

subclmical rheumatic mfection m this type of case the authors beheve that an occasional person may have a pro longed conduction time which is normal for that person and perhaps associated with individual variation of vagal tone

Effect of atropine on conduction time was studied by giving doses of 1/75 gr intravenously to 38 patients In 25 the P R interval returned to normal 13 showed no change Of those not responding six had rheumatic fever four no apparent disease and one each neurocirculatory asthenia gonorrhea and congenital heart disease It is believed that return to normal conduction time after admin

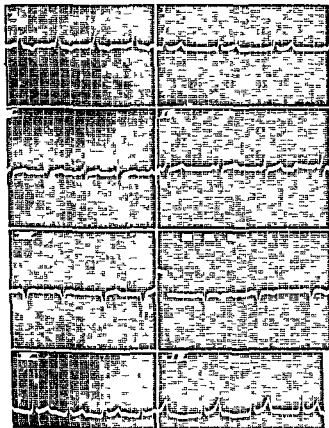
\GE RATE P R INTERVAL AND ATROPINE RESPONSE OF 100 CASES OF FIRST DEGREE HEART BLOCK

Disease	Age	Rate	P R Interval										Atropine	
			2	23	4	6	28	32	34	36	40	44	Pos	Neg
A th t (5)	6 29	68 11	2		2	1								
Art scle o														
Coronary (12)	24 60	60 110	5		5	1					1			
G e l d (2)	44 45	88 90	1		1								1	
D g tal (2)	47 56	70 90												
Con hea (8)	1 29	70 83	3		2		3						4	1
Hyp ten (1)	30	100					1							
Inf ct														
d se se (5)	27	60 100	1				1			1				
M scell (11)	18 53	60 1 0	3		7						1		1	1
N ro l t y														
th (7)	38	60 1 0			4		1						3	1
No d ease (19)	1 55	60 100	7		5	1					1		5	4
Rh m t														
f (8)	19 49	50 1 0	10		10	1		3	1			1	7	6
Tot 1			34		43	4	8	3	1	1	3	1	5	1

istration of atropine indicates that the block is of vagal origin However disappearance of auriculoventricular heart block after atropine does not mean that there may not be pathologic change in the heart muscle or conduction system causing the block Heart block in acute rheumatic fever and other acute infections is often relieved by atropine Possibly in such cases there is some change of vagal tone through altered physiology at the myoneural junction Carter and Dieuaide reported a case of recurrent complete heart block in which the P R inte l returned

to normal with atropine yet examination of the heart after death disclosed a badly diseased bundle

Short P R Interval Associated with Prolongation of QRS Complex Oscar A Palatucci and James E Knighton (M C U S A) report four cases in young healthy men



Fg 83 (l ft) —O g l l t ca d g m
Fg 84 (ght) —S m ft t f N t b dy d p t y
bythm d lt t f T w

(5) A I t M d 1 58 9 J ly 1944

without organic heart disease (Wolff Parkinson White syndrome) Other characteristics include slurring of the initial ventricular deflection peculiar susceptibility to attacks of paroxysmal tachycardia either supraventricular or ventricular and reversal to normal electrocardiographic pattern either spontaneously or after exercise or atropine administration Use of atropine resulted in reversion to a normal tracing in one case and no appreciable effect in two in the remaining one a paradoxical effect was demonstrated (Figs 83 and 84) with bradycardia and respiratory arrhythmia Marked T wave variations were also seen especially in limb leads both spontaneously and after atropine One patient showed a premature contraction fulfilling the criteria of a ventricular extrasystole

The most plausible and generally accepted explanation of this condition is that proposed by Wolferth and Wood that ventricular asynchronism is due to premature stimulation of one ventricle through an abnormal conducting pathway

Electrocardiographic Study of 30 Wounds of the Heart and Pericardium L Herve and A Lorero Sarabia[6] present a clinical and anatomicopathologic study of 27 patients with heart injuries and 3 with injuries of the pericardium and relate findings to electrocardiographic anomalies

During the first 15 days after operation for injuries of the heart and pericardium the electrocardiographic changes are similar to those of acute pericarditis and are due to hemopericardium or pericarditis which are always present in these cases When the pericardial inflammation has subsided signs appear that may be interpreted as dependent on myocardial injury i e inversions of T_1 T_2 and T_4 with injuries of the left ventricle and inversions of T_2 and T_3 and sometimes T_4 with injuries of the right ventricle

Immediate localization of heart injuries is possible only when there is no pericardial lesion or when injuries of the bundle of His (intraventricular block) have been produced This however is rare Injuries of the left

(6) Med B A 3 387 414 J ly 1943

ventricle produce localizing signs more frequently more definitely and more consistently than do injuries of the right ventricle Auricular injuries frequently cause transitory anomalies of the P wave which accompany the signs of pericarditis in the ventricular complex

The uncertainty in localization of myocardial injury during operation may account for discrepancy between clinical data and electrocardiographic changes Death occurred in 11 of the authors cases The complications usually are due to infection and anemia Postoperative course is irregular sometimes being prolonged for weeks Those who escaped complications were able to leave the hospital in good condition 15–20 days after operation

The authors conclude from this study that the electrocardiogram has no prognostic value in injuries of the heart and pericardium

Electrocardiogram and the "Two Step Exercise In many cases of coronary artery disease with angina pectoris the physical examination the size of the heart and cardiac pulsations as seen in roentgenograms and fluoroscopically and the electrocardiogram are normal There is thus no objective evidence to confirm diagnosis of coronary sclerosis Patients with valvular disease often complain of symptoms such as dyspnea and pain although physical examination reveals no evidence of heart failure In both types of cases a functional test i e one that records the response of the heart to effort may be of great value in both diagnosis and evaluation of functional capacity Master developed a test utilizing the response of the blood pressure and pulse rate to a standard two step exercise This measurement of vasomotor response was found to be a practical indication of circulatory fitness Later the electrocardiographic findings following this standard two step exercise were used to reveal the state of the coronary circulation If coronary insufficiency existed characteristic changes occurred in the electrocardiogram No changes appeared in the presence of adequate coronary circulation

A M Master S Nuzie R C Brown and R C Parker

Jr (Nat l Naval Medical Center Bethesda Md) report results which definitely show that the abnormal changes in the electrocardiogram following the two step exercise (Master) are due to lack of oxygen supply to



Fig 85 —Set p w th t da d two-st p h 9 h gb ECC m h Ad o da k h w th w d m t h n phys c w th st p wat h l d bje t t b t t d w th l t od st pp d nd bl od pr ff d g ge bo d a nd a m.

the heart muscle i e coronary insufficiency Whenever electrocardiographic changes appeared after the two step (e g RS T depressions or T wave inversions) they were reproduced exactly in the same subject by his breathing

(7) Am. J M S 207 435 450 Ap 1 1944

10 per cent oxygen When no electrocardiographic abnormalities appeared after the two step none appeared on breathing 10 per cent oxygen

Equipment required for the test is shown in Figure 85 The exercise must be standardized for age and weight since changes occur in normal people if the effort is excessive Tables giving the number of trips to be performed by normal persons according to sex age and weight have been prepared In normal persons blood pressure and pulse return to within 10 points of resting levels in 1½ minutes The following changes in the electrocardiogram *after the two step are considered abnormal depression of* the RS T segment of more than 0 5 mm in any lead and change from an upright T wave to an iso electric (flat) or inverted T wave or T wave changes in the opposite direction

In patients with coronary heart disease the test is of particular value in detecting coronary insufficiency when it is latent In valvular disease the test discloses the state of cardiac function and whether cardiac output is adequate for the coronary arteries In patients with hypertension the control electrocardiogram often shows evidence of coronary insufficiency and therefore may not change after exercise There is a lag in return of blood pressure and pulse following the two step exercise in persons with effort syndrome and the electrocardiogram gives evidence of anoxemia of the heart muscle following exercise In this syndrome the authors believe there is a congenitally small hypoplastic heart which is inadequate on effort

Combined Electrocardiography Stethography and Cardioscopy in Early Diagnosis of Heart Disease is discussed by Walter M Bartlett and J Bailey Carter (Atlanta Ga) A synchronized heart sound tracing and electrocardiogram as an aid in diagnosis presents distinct advantages allowing better correlation with clinical findings Portable equipment permits the physician at the bedside (Fig 86) to substantiate or correct his clinical

(8) A I t M d 19 271 85 A g t 1943

impressions and this objective aid greatly increases clinical accuracy especially in early heart disease It is readily applicable to routine examination of recruits screening of large populations and bedside consultation practice

Results of combined electrocardiography stethography and cardioscopy in examination of 1 108 persons with heart disease are reported In more than half the cases the

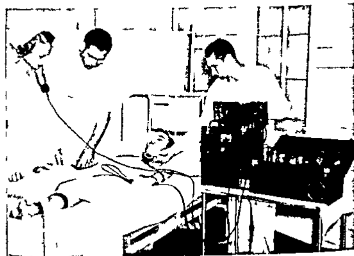


Fig 86—Eq pm t f tak g omb d g aph eco ds llust at g h w nu phys an may l t n t h t sou ds nd m mu thro gh the mpl fy g t th ope Afte nt ty is p operly adj ted it i ften po ble t he m mu m d by u al st c t th s p tech (Ph tog ph by S g l Co p U S Army)

electrocardiogram gave valuable information in more than one third the stethogram was helpful Hence these graphic methods were of value in three out of four cases Graphic methods are useful in differentiating organic and functional murmurs A stethogram is essential for accurate diagnosis of gallop rhythm Of 102 cases of gallop rhythm 42 per cent were misjudged clinically in regard to timing the extra sound Serial stethograms like serial electrocardiograms are useful in following the course of heart disease especially in cases of acute corona [illegible] sion

coronary sclerosis active rheumatic endocarditis subacute bacterial endocarditis and patent ductus arteriosus as well as in obesity hypertension and anemia

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TREATMENT

Curable Forms of Heart Disease comprise only a minority of cases of heart disease but diagnosis is most important as A Stone Freedberg and Herrman L Blumgart (Harvard Univ) emphasize since treatment is highly effective in most cases of these types

In patent ductus arteriosus ligation has proved useful *in many cases and demonstration that the patent ductus is* interfering with normal growth and presence of subacute bacterial endarteritis are regarded as definite indications for the operation Operation should be strongly considered in other cases to prevent progressive overwork of the heart and bacterial endarteritis in a young person Cardiac enlargement due to dilatation disappears rapidly after operation hypertrophic enlargement changes little in the immediate postoperative period but cardiothoracic ratio eventually becomes normal Patients with definite congestive failure preoperatively show no symptoms of failure *postoperatively Mortality of operation is low*

Superimposed infection in patent ductus arteriosus is fatal in 20–40 per cent of all patients in whom the condition is recognized Diagnosis is based on patent ductus arteriosus generalized toxemia and symptoms of bacterial endocarditis Highest percentage (approximately 67) of recoveries follows chemotherapy and surgery together When intensive sulfonamide treatment does not eliminate infection within two weeks surgical ligation of the ductus is indicated Contraindications to surgery are evidence that the patent ductus compensates for a coexisting congenital cardiovascular *anomaly and that vegetations have* spread to aortic or mitral valves

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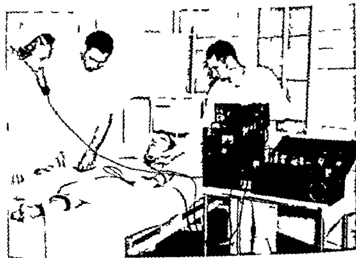


Fig 86—Eq pm nt f t k g omb ned g ph c d ll t al g h w n phy n m y l t n t h t so d d m mu t th gh th ampl fy ng t th cope Aft t n ty p pe ly dju t d t i ften po bl t h m mu m ed by ual oust t th p tech c (Ph tog ph by S g l C p U S A my)

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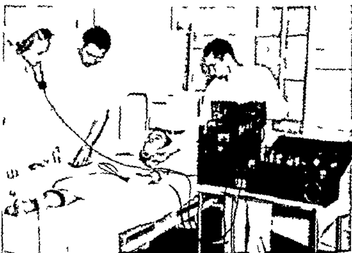


Fig 86 — Eq pm nt f tak g mb d g aph d llu t at g h w nu se pby n may l t n t b t d and m m thro gh th mpl fy ng t th cop Aft t ty p ope ly dj t d t a often pos bl t b m mu m d by ual a t c t thos p c tech c (Ph tog ph by S g l C p U S A my)

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compression According to the Army formula for treatment of penetrating heart wounds blood must be aspirated from the pericardium by the costoxiphoid route if possible within two hours of onset of tamponade after anesthetizing the skin and underlying tissues with 1 per cent novocain If the needle touches the heart a scratching sensation is felt and it must immediately be slightly withdrawn Paracentesis may be done at the site of injury if indicated since withdrawal of even a little blood may be life saving Recurrence of tamponade is indication for a second paracentesis this should not be done less than 15 minutes after the first so that closure of the wound by a clot is favored If tamponade again recurs extrapleural cardiorrhaphy is indicated Mortality rate from this operation in experienced hands varies from 26 to 50 per cent

Contusion of the heart may result from nonpenetrating trauma There may be absence of symptoms with complete recovery delayed fatal rupture of the heart myocardial failure both transient and persistent hemopericardium ruptured valve coronary thrombosis and acute myocardial infarction angina pectoris both transient and persistent and arrhythmias both transient and persistent particularly auricular fibrillation Absence of bruising or other external evidence does not exclude heart trauma Bed rest oxygen administration sedation and paracentesis may result in complete clinical recovery

Cardiovascular syphilis can be prevented in 99 per cent of patients by energetic treatment of early syphilis adequate treatment of cardiovascular syphilis is effective only before serious complications arise Diagnosis of uncomplicated syphilitic aortitis is based on teleroentgen and fluoroscopic evidence of aortic dilatation tympanitic bell like tambour accentuation of the aortic second sound history of circulatory embarrassment progressive cardiac failure substernal pain paroxysmal dyspnea systolic aortic murmur and increased pulsation in the episternal notch Eighty eight per cent of patients with aortic syphilis

Although thiamine deficiency is a well recognized cause of congestive heart failure it is not so widely known that deficiency states may exist with congestive heart failure due to intrinsic cardiac lesions Anorexia dietary limitations anoxia and gastro intestinal congestion causing impaired absorption and possibly deficient storage and utilization of vitamin B with impaired liver function combine to cause vitamin B deficiency in many patients with congestive failure Symptoms are red tongue cheilosis and absence or diminution of tendon reflexes and vibratory sense in the legs Thiamine deficiency results in increased cardiac output blood volume and oxygen consumption decreased circulation time and elevation of venous pressure Vital capacity is low blood pressure may be normal Electrocardiographic changes are noted in almost all patients consisting of tachycardia change in direction of T waves and prolonged QT interval These tend to disappear after adequate thiamine administration suggesting functional disturbance However thiamine deficiency may be followed by focal myocardial necrosis and cardiac hypertrophy In cardiac cases associated with vitamin B deficiency favorable effects were obtained with parenteral administration but no striking benefit was obtained after administration of large amounts of vitamin B complex including thiamine by mouth

Chronic constrictive pericarditis is recognized by presence of a small or only slightly enlarged heart diminished heart tones increased venous pressure and enlarged liver with ascites Approximately 60 per cent of patients may be cured by excision of portions of the scar If the disease is not progressive and disability is mild salt restriction diuretics and tapping of serous cavities are sufficient Digitalis is of no value except when myocardial weakness or auricular fibrillation is present

With heart trauma early recognition of cardiac tamponade is important A large quiet heart increased venous pressure or rapid pulse drop in blood pressure with low pulse pressure cyanosis and orthopnea are signs of cardiac

Proper management of acute cardiovascular emergencies constitutes a serious problem in modern medicine because of frequent occurrence and dire consequences of improper treatment The chief role of the physician who is called first is to determine whether the patient has had a heart attack or some condition simulating it Acute coronary thrombosis and certain abdominal disasters such as perforation of a peptic ulcer or the gallbladder may resemble each other so closely that great skill experience and judgment are necessary to make the diagnosis Such differentiation may be crucial for though immediate operation is the life saving measure for an abdominal catastrophe it would probably cause death of the patient with coronary thrombosis

Regardless of his specialty any physician may be summoned to administer first treatment in case of a cardiac emergency The general practitioner not the heart specialist is usually called in such dire need and his role is of utmost importance In addition to the violent emergency of coronary thrombosis there are other cardiac emergencies of more innocent nature These include angina pectoris (indicating less severe coronary disease) and cardiac irregularities such as paroxysmal tachycardia auricular fibrillation and extrasystole and congestive heart failure

In addition to the simple procedure outlined in immediate treatment of these emergencies Murphy emphasizes that disease of the heart is as much a psychic disorder as a somatic one Fear of death and especially of sudden *death is a feature of heart disease One of the best thera*peutic aids is encouragement to the patient by speaking and acting in a way to inspire confidence and optimism

Indications for Drug Therapy in Heart Disease are outlined by Stewart U Page (Toronto) under (1) digitalis type drugs and quinidine (2) diuretics (3) vasodilators and (4) opiates

Digitalis Type Drugs—Use of digitalis is largely restricted to patients with congestive heart failure irrespec

(2) C d M A J 49 195 00 S pt mb 1943

have a positive serologic reaction Each patient presents an essentially individual problem in treatment

Some patients particularly those over 50 with thyrotoxic heart disease may be apathetic listless and weak rather than overactive Stary eyes marked intolerance to heat rapid auricular fibrillation refractory to digitalis and excessive weight loss are suggestive and indicate studies of metabolic rate Occasionally the syndrome simulates rheumatic heart disease with mitral stenosis because of rough apical systolic or diastolic murmurs or both with a snapping first tone Normal or rapid circulation time in patients with congestive heart failure also suggests thyrotoxicosis although congestive failure due to thiamine deficiency may also be associated with normal or rapid circulation times Preoperative care of thyrotoxic heart disease involves reduction of metabolic rate and thus heart work by rest in bed and iodine and increased heart efficiency by treatment of congestive failure

An erroneous diagnosis of heart disease is often made in patients with anemia because of dyspnea easy fatigability weakness precordial pain murmurs simulating those of mitral stenosis and edema It is sometimes difficult to differentiate dyspnea due solely to inadequate circulating hemoglobin from that due to congestive failure in a severely anemic patient Presence of rales orthopnea and venous engorgement in the latter and their absence in the former are helpful Transfusions iron liver and bed rest result in cure in almost all cases whether symptoms are those of congestive failure or of angina pectoris indicating that heart changes induced by anemia are functional rather than organic Although bed rest may not be necessary in some cases of congestive failure its use with digitalis and diuretics may be required to tide the patient over until hemoglobin level increases significantly in response to antianemic therapy

Treatment of Cardiovascular Emergencies in the Home is discussed by Francis D Murphy[1] (Marquette Univ)

(1) W sc M J 42 769 7 4 A g t, 1943

by a simultaneous single oral dose of digitalis (6–8 cat units) followed by subsequent digitalization Ouabain can be used safely in patients with auricular fibrillation as the ventricular rate furnishes a guide to its effect but greater care is necessary when it is used in presence of regular sinus rhythm

There is insufficient proof that any of the digitalis substitutes or purified factors are more valuable than the standard leaf

Urginin is a mixture of glucosides A and D of squills whose effect when administered orally in congestive failure is similar to that of digitalis It offers no advantage over digitalis except for patients who cannot tolerate digitalis

Quinidine —Much attention has been paid in the past to contraindications to quinidine therapy probably because of the frequency of embolism Its scope has recently widened it has a special place in treatment of young persons with idiopathic auricular fibrillation without other evidence of heart disease Best results have been reported in patients who have had auricular fibrillation for no more than a month Quinidine should also be used when auricular fibrillation is caused by hyperthyroidism in paroxysmal auricular tachycardia and auricular extrasystoles and in coronary thrombosis to prevent onset of ventricular tachycardia and ventricular fibrillation

Diuretics —In congestive failure use of diuretic drugs such as purine derivatives mercury and certain salts is indicated when edema and dyspnea persist after a regimen of digitalization and rest and restriction of fluid and salt intake If there is no great urgency and no nausea and vomiting xanthine should be tried by mouth with later resort to mercurials if necessary Theophylline derivatives (which include aminophylline) are the most efficient diuretics of the purine group but are more toxic and more likely to produce irritation of the stomach than theobromine derivatives which possess slightly less diuretic effect In addition to its diuretic value in congestive heart failure

tive of rhythm or etiology It is however often inefficient failing completely in some cases The most consistent results are undoubtedly obtained in rheumatic auricular fibrillation and the difference in response of heart failure to digitalis lies between this condition and all other kinds of heart failure irrespective of rhythm

Digitalis should not be given for mere breathlessness which may be due to chronic bronchitis asthma emphysema nervousness with sighing respirations or obesity Cardiac dyspnea is of pulmonary origin being caused by reflex stimulation from congestion of the pulmonary circuit Significance of pulmonary emphysema or chronic bronchitis as sole or contributing factors must be evaluated before digitalis is administered As a corollary dyspnea is not an early symptom of all forms of heart disease

Cyanosis is not necessarily an indication for digitalis since it often is due to pulmonary rather than to heart disease Nor is auricular fibrillation an immediate indication for digitalis this is particularly true in old persons in paroxysmal fibrillation and in thyrotoxicosis In treatment of rheumatic heart disease in children digitalis is not very important Fibrillation is uncommon and the fact that infection is present in the heart renders digitalis of little value in the acute stage but in convalescence it may be valuable In the early stage of coronary thrombosis digitalis is not of value and may be harmful perhaps promoting development of ventricular fibrillation It should not be used for simple tachycardia tachycardia of hemorrhage or peripheral circulatory failure in which heart failure is not present

For rapid effect in severe heart failure strophanthus in its crystalline form of ouabain is valuable but it must not be administered if digitalis has been used within two weeks or if there has been recent myocardial infarction In dosage of 0 25–0 5 mg administered intravenously it exerts an initial effect in 5–20 minutes and a maximal effect in 15 minutes to 1 hour The disadvantage of rapid elimination of ouabain can be avoided by supplementing action

type with greatly prolonged expiration morphine in large doses may help to precipitate acute edema of the lungs *through diminution of the respiratory effort In the presence* of acute pulmonary edema large doses of morphine may prove fatal through too marked depression of the respiratory center

In treatment of acute cor pulmonale of pulmonary embolism papaverine hydrochloride (or eupaverine a less toxic derivative) has a beneficial effect attributed to relaxation of spasm in pulmonary arteries and to coronary dilatation Morphine or pantopon may be used additionally for *greater relief of pain Papaverine is also recommended* by some for relief of pain in coronary thrombosis of the aged

Some Therapeutic Fallacies are discussed by J W Linnell and W A R Thomson Few patients in middle life who suffer from essential hypertension would have symptoms referable to this condition if they had not been *informed that they were its victims Dizziness sense of ful*ness in the head and occipital headache are nearly always due to anxiety largely dependent on knowledge of blood pressure height Despite many theories the cause of hypertension is unknown and contrary to common medical belief general or local infections auto-intoxication derived from the bowel prolonged physical strain and a high protein diet have nothing to do with it Nervous strain may raise blood pressure temporarily but there is no evidence that it can produce *hypertension Endocrine disturbances* are easily blamed they are harder to incriminate

Although it is impossible to reduce blood pressure except temporarily prolonged rest in bed regular purgation repeated venesections diets of many kinds baths scores of drugs and organic extracts high frequency currents diathermy and many other procedures are constantly being used With *present knowledge it is more logical to ap*proach the treatment philosophically There is no need to tell a patient he has high blood pressure for he may then

(3) B M J 2 572 57 Nov 6 1943

especially when combined with salyrgan aminophylline has considerable value as a respiratory stimulant

There is increasing recognition of the value of mercurial diuretics in treatment of heart failure even in absence of obvious edema *In cases with little or no peripheral edema* but with dyspnea and signs of pulmonary vascular congestion despite full digitalization a mercurial will frequently bring relief The commonly used preparations esidrone mersalyl neptal and salyrgan all contain theophylline which prevents necrosis at the injection site and promote more rapid and complete absorption and greater diuretic effect

Vasodilators—Value of xanthines as vasodilators is controversial Some investigators accord theophylline and theobromine and their derivatives considerable value as vasodilators in the early stage of coronary artery disease despite some criticism by others over their failure in certain cases of angina Among the nitrites nitroglycerin is undoubtedly still the best There is a limited field of use for longer acting nitrates such as erythrol tetranitrate and mannitol hexanitrate due to frequency of side effects. Quinidine sulfate has been used in prevention of attacks of angina pectoris although the rationale is not clear Digitalis is rarely of value in angina pectoris and in some cases causes striking increase in frequency of attacks Coramine does not seem to have a direct action on cardiac efficiency Its favorable action on respiratory distress seems to be due to several possible causes such as respiratory stimulation of the respiratory center reduction of intrathecal pressure relief of cerebral venous engorgement etc

Opiates—Opinion varies as to dosage of opiates in acute myocardial infarction Some give large doses immediately others claim that smaller doses are safer advising just enough morphine to dull the pain and relieve breathlessness In paroxysmal cardiac dyspnea morphine sulfate (1/6–1/4 gr) depresses the respiratory center allays anxiety and restlessness relieves dyspnea and cough and lowers blood pressure With respiration sthmatic

serious myocardial disease is present most cases indeed follow an attack of coronary thrombosis Digitalis is almost certainly ineffective and in large doses may be harmful whereas quinidine sulfate orally or intravenously may produce most dramatic benefit More commonly the tachycardia is *supraventricular in origin* either auricular or nodal Here prognosis usually is excellent for in most patients the myocardium is healthy Unless the life of the patient is crippled through frequency or length of attacks or cardiac reserve is diminished active treatment is unnecessary except for rest during the attack A small number of patients can stop an attack by pressing on the carotid sinus holding the breath inducing retching adopting a certain posture etc If it is deemed advisable or necessary to stop an attack a subcutaneous injection of acetyl beta methylcholine chloride is most likely to be successful but its effects in other ways may be alarming Digitalis neither stops paroxysms nor diminishes their incidence and quinidine sulfate is usually not effective

Marvelous as is the effect of digitalis in most cases of established auricular fibrillation it will not stop individual attacks of paroxysmal auricular fibrillation nor is there satisfactory evidence that its regular administration prevents such attacks In themselves these attacks are usually harmless but if it is considered necessary to stop them quinidine sulfate orally at frequent intervals is effective Since thyrotoxicosis is a frequent cause a goiter should be searched for in every case

Drugs such as strophanthin and digitalis have no place in treatment of shock which is due to vasomotor and not cardiac failure

Although calcium is widely used in hemorrhagic diseases and before operation as a prophylactic against hemorrhage there is no pharmacologic evidence that it either increases coagulability or shortens bleeding time There is no justification for using it in these conditions and preoperatively it is of value only in cases of obstructive jaundice in which however vitamin K is more important

live in constant dread of a stroke If he has been told already why not reassure him and tell him of persons with high blood pressure who are leading active lives? As long *as there are no complications* the patient should *not* be allowed to consider himself an invalid but should be advised to avoid undue physical and mental strain He should be encouraged to take moderate outdoor exercise to control *insomnia and to reduce weight* if necessary

Recently there has been an increasing tendency to diagnose low blood pressure in cases in which no organic cause can be found for a patient s complaints and thus a *new invalid is created* Except *in a few conditions* such as shock severe hemorrhage Addison s disease coronary thrombosis and severe infection hypotension has no clinical significance

Much effort is wasted in attempts to treat arterio clerosis for which there is no known treatment No useful purpose is served however by telling a patient that he has it He will profit most from encouragement

Many drugs including sodium nitrite mannitol hexanitrate erythrol tetranitrate potassium iodide luminal chloral morphine papaverine phenacetin diuretin euphyline belladonna digitalis lacarnol and harmol are uselessly employed in angina pectoris Nitrites particularly a freshly prepared glyceryl tetranitrate tablets dissolved rapidly in the mouth are of great value in relieving and in preventing attacks if taken immediately before exposure to conditions likely to induce them So transitory is their effect however that to give them regularly i e three times a day to prevent attacks is even less reasonable than to inject adrenalin three times a day to prevent asthma attacks

To some practitioners mere presence of a bruit or tachycardia is indication for digitalis but the single indication for digitalis is heart failure in some degree In paroxysmal tachycardia the first important step is an accurate diagnosis *If the tachycardia is of ventricular* origin prognosis usually is grave since in [illegible] patient

produced Adequate digitalization can usually be obtained in cardiac failure by administration every six hours of such preparations as tablets of Digitalis folia (1 gr) digitalin (1/600 gr) or Digitalis composita each of which is roughly equivalent to 10 minims of standard tincture The 0 25 mg tabloid of digoxin is reckoned to be equivalent to 15 minims of standard tincture

[If digitalis is indicated, *full* digitalization should be carried out immediately That means usually a total equivalent to approximately 18–20 gr whole leaf in 24–48 hours Then the average maintenance dose hould be 1½ gr per day —Ed]

Mercurial diuretics are indispensable when digitalis fails to relieve cardiac dropsy Following intramuscular or intravenous injection they usually promote effective dehydration within a few hours In case of toxic symptoms the drug can be used in suppository form or as tablets for oral administration

The primary objective of treatment of *angina pectoris* is to plan the routine of patients lives and habits in strict conformity with their diminished reserve to correct obesity by physical therapy and dietetic measures and to prescribe drugs to diminish the liability to anginal attacks These include xanthine diuretics iodides nicotinic acid and sedatives Anginal attacks which frequently complicate myxedema may be alleviated by thyroid medication Surgical procedures such as cervical sympathectomy paravertebral injections of alcohol into the upper thoracic sympathetic ganglions thyroidectomy and myocardial grafting operations have had experimental trial with results that warrant further development

The basis of treatment of coronary occlusion is complete rest for a month or longer if the condition is of average severity First essentials are relief of pain and alleviation of prostration and shock which occur in early stages A hypodermic injection (1/2 gr) of morphine with atropine (1/1000 gr) should be given as soon as possible and further doses (1/4–1/6 gr at four to six hour intervals) may be administered to relieve such pain and soreness as may persist and to insure the required

Thousands of persons are treated for anemia who are not anemic since clinical diagnosis of anemia is likely to be fallacious Most anemic patients with a low color index are benefited by iron if effective preparations are used in adequate dosage In this connection the recent fashionable craze for giving iron by injection is deplorable Vaughan's dictum that intravenous intramuscular and all proprietary preparations of iron are as useless as they are expensive is practically true Liver is not a panacea for every type of anemia With rare exceptions it is valuable only in treatment of pernicious anemia and other megalocytic anemias Parenteral therapy is infinitely preferable to oral Dilute hydrochloric acid seldom relieves any accompanying indigestion and has no effect on the anemia There is no evidence that arsenic is of value in treatment of either microcytic or megalocytic anemia

That subtotal thyroidectomy is the best treatment for toxic goiter is now firmly established Iodine does not cure and this cannot be stressed too strongly Its amelioration of signs and symptoms is only temporary and its use should be restricted to the periods immediately before and after operation when it contributes greatly to surgical safety The common practice of giving iodine for months and even years in the belief that it cures is strongly condemned for thereby operation often is postponed until cardiac complications extreme emaciation or psychosis supervenes

Cardiovascular System Treatment of various diseases of the heart and vessels is reviewed and summarized by B T Parsons Smith[4]

The effective scope of digitalis therapy has materially narrowed Irrespective of its pathology congestive heart failure is the one outstanding indication for digitalization particularly with arrhythmias of the fibrillation or flutter types also in cases of normal rhythm The modern view is to prescribe small or medium dosage the amount being determined in each patient according to specific effects

(4) Pr ct t 151 71 6 No mbe 1943

valvular lesions Touroff advised that patients with patent ductus arteriosus should be kept under observation that a blood culture should be taken if an obscure fever develops and that operation should be undertaken as soon as the diagnosis of superimposed infection is established

The results of chemotherapy have been generally disappointing in bacterial endocarditis though isolated cures have been recorded A small number of patients recover spontaneously Treatment should be based on such essentials as rest skilful nursing fresh air sunshine suitable hematinics and blood transfusions with addition of appropriate supportive and symptomatic remedies as required

Reliable signs of constrictive pericarditis include a fixed apex impulse a small pulse of paradoxical type, raised venous pressure with cyanosis peripheral edema enlargement of the liver and recurring ascites and low voltage ventricular complexes on the cardiogram Radiologic investigation is usually valuable in diagnosing the condition If conditions are otherwise favorable the rational treatment of constrictive pericarditis is pericardial resection with which encouraging results have been achieved

Abuse of Rest as Therapeutic Measure for Patients with Cardiovascular Disease According to Tinsley R Harrison (Southwestern Med College) many hypothetical advantages are claimed for prolonged rest in bed following myocardial infarction (1) Liability to cardiac rupture probably especially important during the first two weeks is decreased (2) Aggravation of cerebral anoxia by the upright position during circulatory collapse is prevented However in most patients serious circulatory collapse has disappeared in a week or two and hence from this standpoint there is rarely need for more prolonged rigid rest (3) Prolonged rest leads to a firmer and smaller scar This can be questioned because cardiac work per beat is probably no greater and may be somewhat less in the sitting than in the recumbent posture Theoretical disadvantages are also advanced (1) Given a tendency

(5) J A M A 125 1075 1077 A g 19 1944

degree of physical and mental quietude Congestive heart failure and uncontrolled auricular fibrillation are indications for digitalis but the drug must be administered with caution for patients with coronary thrombosis are likely to develop ventricular tachycardia for which digitalis is known to be responsible Quinidine in relatively large dosage is the recognized treatment for ventricular tachycardia Cook and White advise 3-6 gr doses every two to three hours until the paroxysm ceases or signs of intolerance appear and a maintenance dose of 3-6 gr daily for three months subsequently

Diabetes in a cardiac patient must not be treated as a pure problem of diabetic stabilization Smith concluded after exhaustive research that it was safer for such patients to live with a moderate degree of hyperglycemia than to be strictly controlled and rendered constantly sugar free Insulin should be used to control severe hyperglycemia and abolish acetonemia

Hypertension has been recognized as a symptom and not a disease and empiric treatment has been superseded by therapy based on an etiologic background Renal antipressor therapy and surgical measures such as resection of splanchnic nerves and lumbar ganglionectomy have yielded promising results

In obliterative vascular disease of the lower extremities medical treatment including vasodilators saline injections serum therapy contrast bathing intermittent venous occlusion paevex boot and Buerger s exercises should be used Some good results are obtained though improvement often is transitory and relapses frequent Surgical treatment particularly lumbar sympathectomy has been increasingly advocated during the past few years

Although recovery has occurred following chemotherapy in certain cases of patent ductus arteriosus complicated by subacute bacterial endarteritis the trend of modern opinion favors ligation or division of the ductus assuming that the condition is not associated with other congenital anomalies and that there is no evidence vegetative

except in patients especially liable to immediate development of myocardial infarction as indicated by increasingly frequent and prolonged attacks at rest In all patients with severe forms of heart disease activity should be kept below the symptomatic threshold i e less than that which induces dyspnea or pain

Evil Sequelae of Complete Bed Rest. William Dock (Univ of Southern California) says that it must be recognized that many disturbances of function such as massive collapse of the lung attributed to operation illness anesthesia or medication become evident only because the patient was forced to spend hours or days in the dorsal recumbent position Bone atrophy muscle wasting and vasomotor instability are frequent sequelae of bed rest while constipation cathartic habituation backache and many other chronic disabilities may appear during bed rest and persist for years Obstructive uropathy or pulmonary edema occurs too frequently in elderly patients confined to bed

If the patient lies flat at all times venous pressure is low and caliber of the veins small In abdomen pelvis and legs veins then are much smaller than when the patient is sitting up With veins at this small caliber velocity of blood flow will be high despite decreased volume of flow when the shoulders are propped up veins of the pelvis and legs are dilated and velocity of flow correspondingly reduced possibly to one tenth that when the veins are in the same plane as the heart Veins compressed and empty due to pressure of the leg against the bed may easily suffer endothelial damage and begin to thrombose while still nearly empty Only when the patient is sitting or standing are these veins constantly dilated to their full caliber but during coughing or bearing down to facilitate expulsion of flatus feces or urine transient maximal venous dilatation may occur Formation of large clots propagated far along the system is made possible by prolonged absence of sighing respiration cough or bearing

(6) J A M A 125 1083 1085 A g 19 1944

toward development of congestive heart failure edema of the lungs tends to occur more readily in the recumbent position (2) Rigid restriction of activity reduces flow of blood to a minimum and may tend to favor development of thrombi either in the venous system with subsequent pulmonary infarction or in the arteries and more especially in branches of the coronary system other than the ones originally affected Hence both pulmonary infarction and a second myocardial infarction frequently occur in patients subjected to unusually prolonged and rigid rest (3) Hypostatic pneumonia is especially likely to occur in elderly persons who remain in bed a long time

Review of recent experimental evidence and certain clinical considerations leads to several general conclusions Extreme restriction of body movement causes increased mortality in animals with experimental myocardial injury There is no proof that rest in bed for many weeks after symptoms have disappeared is valuable in physical management of the patient with congestive failure angina pectoris or myocardial infarction Available evidence while perhaps inconclusive points to the contrary more especially if the recumbent posture is enforced while the patient is kept in bed From the psychic standpoint there is a definite disadvantage in enforcement of a rigid regimen after the acute phase of the illness has subsided. Until more definite information is available Harrison suggests a plan of treatment to be modified according to status of the patient Persons with congestive failure should be allowed out of bed for several hours a day as soon as severe dyspnea at rest has subsided Following myocardial infarction recumbency should not be prescribed longer than two or three weeks after the more acute and alarming symptoms have subsided. The recumbent position should not be enforced on patients who are more comfortable sitting Other things being equal elderly patients should be allowed out of bed sooner than younger ones Rest in bed for more than a day or two at a time probably has no place in treatment of angi[illegible] ectoris

the pillows Patients with difficulty in urination or defecation probably undergo less risk if they are warned against this procedure and allowed to get out of bed to use a commode

Therapeutic measures necessary to minimize hazards of complete bed rest include omission or rigid restriction of narcotics and sedatives encouragement of deep breathing exercises frequent changes of posture and acceleration of venous flow in the legs by elevating the foot of the bed and not the patient s thorax or by exercise or reaction hyperemia from brief arterial compression Bed rest always highly unphysiologic and definitely hazardous must be ordered only for specific indications and discontinued as early as possible

Optimal Dose of Mercurial Diuretics was determined by Walter Modell (Cornell Univ) in a study on 37 ambulatory clinic patients with chronic congestive heart failure who needed a diuretic Each patient served as his own control and basis for comparison Effects were compared by alternate injections of different doses In the period between injections edema was allowed to accumulate to its former level Weight loss was used as a measure of diuresis

Results indicated that mercurial diuretics in the therapeutic range are relatively more effective as the dose of drug becomes smaller Amount of diuresis depends on amount of edema fluid present When a small dose is given its effect is great because a large accumulation of fluid is available for the entire duration of its action *whereas when a larger dose is given in the same state* most of the edema disappears before diuretic action ceases Very small doses however produce too small an absolute diuresis to be practical Effectiveness of a 1 cc. dose of mercupurin is about 60 per cent greater than that of a 2 cc. dose whether or not ammonium chloride or other supplementary drugs are used Absolute difference in total effect between the two sizes of dose for the entire

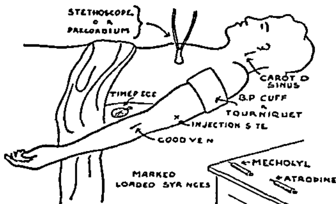
(7) A n. I t. Med. 20 265 274 Febru ry 1944

down and by constant elevation of the heart above the pelvis Dislodgment of clots with formation of emboli occurs with a sudden rise in venous pressure. As the wave of pressure and venous distention sweeps outward along the venous system loosely adherent clots formed in collapsed or partly dilated veins are dislodged If veins are dilated frequently propagation of clots is almost impossible as the thrombi are dislodged from minute vessels in which clot formation begins Patients with acidosis uremia anemia or impaired blood coagulation who get up several times a day or have severe cough therefore are much less subject to serious vascular accidents during bed rest either because clots form and grow less readily or because they are dislodged before they become large The greatest hazard exists when the patient is propped up slightly for 8–14 hours daily as this favors clotting in partially distended veins

Patients dying after only a day or two in bed may have airless patches scattered through the dorsal and caudal parts of the lungs Physical signs and roentgen studies indicate occurrence of hyperemia and edema in dependent parts of the lungs especially on the right side probably predisposing to collapse of local regions In these collapsed parts terminal or hypostatic pneumonia develops and necrosis begins whenever pulmonary infarction follows pulmonary embolism

A tremendous strain is put on the heart and circulation by a maneuver which patients in bed frequently perform and against which many are never warned Whenever one takes a deep breath closes the glottis and tightens the thoracic and abdominal muscles (Valsalva s experiment bearing down) there follows a series of extreme fluctuations in thoracic pressure cardiac output blood pressure and vagal and vasomotor tone After myocardial infarction sudden death is far more likely to occur from this effort than from any other cause and it is a common incitant of pulmonary embolism This may occur even when passing flatus or trying to push oneself higher on

tourniquet placed loosely high on the upper arm mecholyl is administered subcutaneously below or distal to the blood pressure cuff which is not inflated The moment heart rhythm and rate return to normal (as detected by a stethoscope over the precordium) the blood pressure cuff is inflated to prevent further absorption and to prepare a vein if desired for administration of atropine Return to sinus rhythm may occur 80 seconds after injection or even less If no effect on rate is noted when the drug reaches peak effect as manifested by flush in the blush areas perspiration salivation and loud peristalsis (2–10 minutes) Starr has suggested massage of



F g 87 —Me h lyl adm ni t t on pat t ecumbent.

the injection site and carotid sinus stimulation by physical means this is necessary in about 20 per cent of cases If no effect is manifest 30 minutes after injection another dose may be given

The drug does not lose its effectiveness by repeated use No deaths have been reported from use of mecholyl but reports are available of great overdose (10 and more times the therapeutic dose) and mistaken intravenous administration and in each instance recovery was complete

Heart Attack and Its Prevention by Operation. Claude S Beck[9] (Western Reserve Univ) advances the concept that the heart attack is similar to a convulsive

(9) P oc. I t t. P tgr d M A N th Am rica, 1943 pp 138 140

series is only about 20 per cent although the increase in dose is 100 per cent Use of ammonium chloride increases diuresis of either dose by about 15 per cent

Distinct advantages may be obtained by giving a patient two 1 cc injections instead of one 2 cc injection a week These include not only a 20 per cent greater total diuresis but greater comfort with less danger to the patient Effects of intramuscular and intravenous injections of the same dose of mercupurin are about the same The intramuscular injection often causes moderate local tenderness but eliminates serious immediate reactions

Management of Paroxysmal Tachycardia, Including Use of Mecholyl Paroxysmal supraventricular tachycardia is common particularly in young adults without organic heart disease but it has been fatal and has led to disabling thrombotic conditions A history of it disqualifies for air crew and flying personnel and electrocardiographic evidence is cause for rejection in candidates for Army commissions but since the first attack may occur at any age it is probable that cases will be observed occasionally in the armed forces Most attacks do not require medical attention but an estimated 10–20 per cent defy the patient s efforts to stop them

Philip W Morgan[8] (Emporia Kans) states that direct therapy usually is not indicated to prevent attacks but reassurance and investigation of psychic factors are indicated Therapy of attacks includes carotid sinus reflex elicitation sedatives and oral quinidine If the last is ineffective digitalis is given orally or parenterally but mecholyl is preferred if parenteral therapy is indicated

PROCEDURE—The patient receiving mecholyl should be recumbent (Fig 87) since the erect posture may cause fainting It is well to give morphine before using mecholyl to dim slightly the perceptive senses Average dose of mecholyl for adults is 20–50 mg Contents of an ampule (25 mg) are readily soluble in 1 cc or less of sterile distilled water Atropine gr 1/50 in solution should be available for injection in a second syringe. A blood pressure cuff is applied or a good

(8) Ann. I t. Med. 19 780 786 November 1943.

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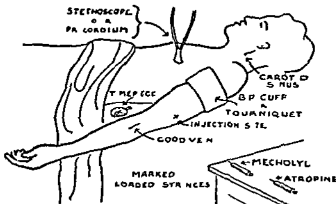


Fig 87 —M h lyl dm t tion patient ecumbent.

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seizure in that it is induced by myocardial anoxemia and that the development of a degree of anoxemia sufficient to precipitate a heart attack is precipitated suddenly, as in coronary disease when the final insult to the myocardial vasculature disrupts the balance necessary for normal myocardial function To obviate the final decrement in blood supply which precipitates the heart attack thereby acting as a trigger mechanism Beck advocates surgical institution of corollary blood supply to the myocardium There are three ways in which this can be done The first is by production of extracoronary communications these are communications between the coronary arteries and the arteries of tissue grafted on the heart The second method is based on the development of inflammation on the heart surface with consequent increased vascularity The third method is to provide time for the occlusive disease to bring about intercoronary channels

The desirable patient for operation is one with little myocardial destruction The operation should be looked on as a prophylaxis rather than as a cure for damage once inflicted Among 37 patients operated on results in those who survived operation were good Many were able to return to work and were relieved of pain

MISCELLANEOUS

Reversibility of Heart Disease Paul D White (Boston) states that 30 years ago it was believed that heart disease was always fatal that coronary arteries were forever end arteries and that at best death could simply be delayed a little and the remaining hours of the patients be made a bit more comfortable About 20 years ago clearcut proof was obtained of reversibility of effects on the heart of thyroid disease of both major types thyrotoxicosis and myxedema through subtotal thyroidectomy and administration of thyroid gland Since then every

(1) Illinois M J 86 9-14 J ly 1944

variety of heart disease has to some degree manifested *reversibility either spontaneously* or under medical or surgical treatment. In 1928 the first patient with chronic constrictive pericarditis was cured by pericardial resection *In rheumatic heart disease the reversibility has been* largely spontaneous although possibly saturation with salicylates orally or intravenously may yet be shown to *play a role Surgical attacks on aneurysms* both saccular and arteriovenous not only abolished hazard from the local lesion particularly of rupture in the former but in *the latter relieved strain on the heart*

During the last decade through growing clinical and electrocardiographic experience and the fundamentally *significant observations of Schlesinger and Blumgart* it has been demonstrated that many patients with coronary heart disease do well after acute occlusion or the first *attack of angina pectoris This is due to development* largely spontaneous of collateral coronary circulation Under the increasing head of pressure the smaller *coronary twigs and their branches become larger and can* usually transport to the myocardium where needed increasing amounts of blood With ordinary luck this hap*pens to the average person as he grows older* there may actually be a complete slow occlusion of a major coronary trunk with no heart disease at all due to this spontaneous *adjustment Thus coronary arterial disease is not to be* confused with coronary heart disease Various medical and surgical measures directed toward stimulating devel*opment of this collateral circulation have not been notably* successful one must realize that nature does the best job but must not omit efforts at therapy

Previously four to five years were the generally cited average survival after the first attack of angina pectoris The author and his associates Bland and Miskall in an *adequate follow up study found that the average ex*pectation of life was actually double that currently taught i e between 9 and 10 years and also that angina pectoris either decubitus or on effort frequently subsides *spon*

taneously when adequate collateral circulation develops

[The article referred to by White Bland and Miskall appears in this YEAR BOOK p 516—Ed.]

Recently further reversible manifestations of heart trouble were clearly defined in cardiac dilatation found in acute hemorrhagic nephritis in B_1 avitaminosis and in severe anemia Active therapy quickly corrects the last two conditions while the nephritic heart abnormality subsides with subsidence of the underlying disease Acute pericardial effusions also may quickly disappear

Since 1938 many patients with patent ductus arteriosus have been successfully treated by surgical ligation This relieves strain on both ventricles which may be considerable in some cases of wide patency and cures some instances of complicating Streptococcus viridans endarteritis with or without additional chemotherapy The operation is dangerous and is not to be advi ed lightly but it constitutes the first successful demonstration of the reversibility of the congenital cardiovascular defects except for the extremely rare instances of spontaneous recovery

In 12 years before 1939 only 1 of 250 patients with subacute bacterial endocarditis in the Boston hospitals recovered he succumbed to another illness a year later With sulfonamide therapy the percentage of cures rose from less than 1 per cent to 5–10 per cent being slightly higher among those who also received heparin Now results of the very recent massive treatment with penicillin give new hope

The last variety of heart disease to show reversibility is the hypertensive heart Improvements of electrocardiograms sometimes complete return to normal have been observed after splanchnic resection as practiced by Smithwick He improved the technic of the former inadequate splanchnic resection by denervating both above and below the diaphragm usually from the eighth dorsal to the second lumbar and always the great splanchnic His success in appreciably influencing the blood pressure and thereby relieving strain on the heart has risen from t about

70 per cent and the results have been holding for years

Age, Change and the Adapted Life William de B MacNider (Univ of North Carolina) states that aging of the animal organism of man commences not at 40 or a similar chronological period but when the spermatozoan unites with and fertilizes the ovum The organism as an individual at birth has so aged that it can attempt to cope *with a changing external environment and by physiologic* changes can effect a functional adjustment designated an adapted and related life Duration after birth for constructive aging toward perfection in adult life varies with the species of animal and with animals of the same species In man certain families age more rapidly than others the individuals reach maturity more rapidly and retrogressive changes supervene at relatively earlier age periods There is as yet no understanding of differences in chemical constitution of tissues of such families which determine advent and rapidity of aging

The age factor whatever it represents in terms of chemical constitution is the determining influence which largely segregates certain infectious processes During infancy and childhood over and above accidents represented by infectious diseases there was formerly a high mortality due to imperfect feeding and nutritional disturbances these in turn certainly predisposed to development of specific infections Understanding in this domain came about not from knowledge of the adult organism but through interest of investigators willing to concern themselves with life processes aging of infants and young children this led to development of the medical specialty of pediatrics The same order of investigation is imperative for individuals who have reached their peak of constructive development and at different chronologic periods commence the descent toward senility These retrogressive changes make their gross not their chemical appearance at what is designated middle age Chemical basis for such changes must develop years earlier Such retrogressive

(2) S en 99 415-419 M y 26 1944

tissue modifications progress with periods of transitory tissue adjustment and maladjustment until the changes become fixed and stabilized as a state of disease or physiologic senility Such states are not reversible though they may represent periods of tissue reaction in an attempt at stabilization

Symptoms and signs of departures from the retrogressive aging normal are varied and variable depending on which organ organ system or tissue expresses itself in such change and their modification variability and intensity and the readiness with which they develop are partly genetic and partly due to metabolic changes in cells The latter should be amenable to use of appropriate diets aided by accurately determined inorganic and vitamin supplements Biochemical and nutritional research for older age groups is imperative for prevention of a considerable proportion of degenerative diseases

Microscopic studies of cell changes are essential for morphologic and anatomic understanding of disease but they afford little understanding of those pathologic life processes which finally assume such chemical intensity as to modify cell structure and demonstrate their presence by physical change the commencement of disease frequently encountered in the middle aged group Pathology physiology and pharmacology of the future will be biochemical and biophysical This is necessary if information is to be obtained of changing chemical life of tissues as they advance from one age period to another and as these periods are modified by departures from the normal With such knowledge these chemical changes within cells can to some extent be regulated and guided not to prolong life into a useless and unhappy senile state but to conserve and protect at periods when such control may effectively relate itself in work for the individual the family and the social and economic order

Unfortunate Prevalence of Formulary Diagnosis in Cardiac Problems is deplored by F A Willius [*] By formu

(3) P oc. Staff M L May Cl n. 18 470-471 Dec.

lary diagnosis is meant the fallacious practice of according universal and unequivocal significance to various symptoms and signs regardless of their relevance to the individual diagnostic problem under consideration Medicine is threatened by mechanization if time tested methods of physical diagnosis are permitted to deteriorate Formulary diagnosis always manifests itself more generally when large groups are subjected to examinations dictated by arbitrary regulations obviously designed to limit individual interpretation by many examiners

With regard to cardiac murmurs the formulary edict is worded to the effect that under all circumstances these murmurs are abnormalities and thereby imply existence of heart disease This is fallacious for many murmurs are physiologic the result of increased circulation rate under certain circumstances of anatomic contact of pericardium and pleura and of other functional occurrences The presystolic or diastolic murmur regardless of its location is virtually without exception significant However the systolic murmur is commonly only of physiologic importance particularly when situated in the pulmonic area and at the cardiac apex The latter murmurs are commonly considered indicative of regurgitation at the mitral valve This interpretation may be correct when the heart is greatly enlarged but in hearts of normal size especially in younger patients without antecedent histories of rheumatic fever and with normal cardiac function diagnosis of mitral regurgitation is usually incorrect In fact uncomplicated mitral regurgitation of endocardial origin is so rare as to be almost a pathologic curiosity Thus acceptance of a murmur as indicative of heart disease without careful correlation with other evidence is easily capable of leading to serious diagnostic error

[It seems a shame that so many children must lead unhappy lives and so many parents must be made miserable by physicians placing unwarranted importance on murmurs in the absence of active rheumatic fever or cardiac enlargement —Ed.]

Other phenomena which likewise may be of only physiologic importance become obstacles when formulary

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Ninety per cent of cases of heart disease and of congestive failure may be diagnosed and treated satisfactorily without the aid of any laboratory work Fluoroscopy in the usual cases of heart disease shows enlargement and the shape of the heart and congestion of the lungs Enlargement can often be determined by physical examination distortions are more difficult to determine but not so important from a practical viewpoint Congestion of the lungs can be established by presence of dyspnea and rales Electrocardiography remains in many cases a luxury and refinement that intrigues the physician more than it helps the patient It sometimes shows an unsuspected bundle branch block in an otherwise healthy person or evidence of coronary sclerosis in a middle aged man even so handling of the case except for admonition of moderation will probably not materially affect the prognosis The electrocardiogram is of great practical value in diagnosis of tachycardia of ventricular origin adequate use of quinidine may be life saving since unless this arrhythmia *is stopped it may precipitate severe congestive failure or* cause sudden death Discarding of electrocardiography is not being advocated it is fine to have an electrocardiogram in every case of suspected or known heart disease and serial studies in myocardial infarction but if tracings are not readily obtainable there should not be too much concern

Estimations of venous pressure and circulation times usually done together are of diagnostic value the former in questionable cases of heart failure suspected cases of constrictive pericarditis mediastinal venous thrombosis and peripheral venous thrombosis and the latter in determining the presence of congestive failure and its degree In congestive failure the venous pressure usually 200 mm water or more rises more than 20 mm with pressure on the right upper quadrant of the abdomen With venous thrombosis this rise does not occur whereas opening and closing the fist of the tested extremity results in great rise of pressure

criteria are operative Simple tachycardia is commonly considered as presumptive evidence of existent cardiac disease even though corroborative symptoms or signs are absent Many perfectly normal persons exhibit tachycardia under the stress of physical examination Hence establish ment of an arbitrary level for heart rate without the opportunity of applying individual judgment is absurd

Minor disturbances of cardiac rhythm such as sinus arrhythmia and premature contractions are sometimes the sole evidence in erroneous diagnosis of heart disease Actually these arrhythmias occur far more commonly in the structurally normal heart than in the diseased organ When heart disease exists the arrhythmia is so over shadowed by other symptoms and signs as to be negligible

Widespread use of electrocardiography has been the most fertile soil for formulary interpretation Electrocardiography is a precise method of examination but clearly a diagnostic adjunct and only a precision method when correlated with symptoms and signs and when its physiologic variations are known and distinguished from simulating pathologic variations Serious heart disease may be present when the electrocardiogram is normal Likewise certain alterations in the electrocardiogram occur when no other evidence whatsoever of heart disease exists Electrocardiographic findings must never be the sole evidence for diagnosis of heart disease

Selection and Interpretation of Laboratory Tests is discussed by Wallace M Yater (Washington D C) Now more than ever economic aspects of medicine are important and by judicious selection and frugal use of simpler and more definitive laboratory examinations good medicine may be practiced more economically and with out overburdening dwindling technical personnel Ex travagance in use of the laboratory results because of lack of knowledge of proper use of its services unwillingness to spend sufficient time in history taking and physical examinations or unbridled scientific enthusiasm

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TABLE 2—Final Diagnoses in Cases Rejected by Special Boards

Diagnoses	No. of Cases: Total Five Cities	Boston	Chicago	New York	Philadelphia	San Francisco	Percentage of Cases Finally Rejected: Total Five Cities	Boston	Chicago	New York	Philadelphia	San Francisco
Total finally rejected	4 131	812	962	808	864	685	100.0	100.0	100.0	100.0	100.0	100.0
Rheumatic valvular heart disease	2 476	415	676	545	569	271	59.9	51.1	70.3	67.4	65.9	39.6
Hypertension	1 059	249	239	159	200	212	25.6	30.7	24.8	19.7	23.1	30.9
Tachycardia	189	32	75	48	8	26	4.6	3.9	7.8	5.9	0.9	3.8
Congenital heart disease	183	45	28	29	18	63	4.4	5.5	2.9	3.6	2.1	9.2
Syphilis of aorta	17	0	5	7	3	2	0.4	0.0	0.5	0.9	0.3	0.3
Aneurysm other than aorta	1	0	0	1	0	0	0.0	0.0	0.0	0.1	0.0	0.0
Cardiac enlargement only	76	12	9	20	9	26	1.8	1.5	0.9	2.5	1.0	3.8
Myocarditis chronic rheumatic	6	0	1	5	0	0	0.1	0.0	0.1	0.6	0.0	0.0
Coronary heart disease	6	1	0	2	0	3	0.1	0.1	0.0	0.2	0.0	0.4
Heart disease unspecified	113	14	28	1	0	70	2.7	1.7	2.9	0.1	0.0	10.2
Neurocirculatory asthenia	204	78	11	31	54	30	4.9	9.6	1.1	3.8	6.3	4.4
Auricular fibrillation paroxysmal	4	1	1	2	0	0	0.1	0.1	0.1	0.2	0.0	0.0
Auricular fibrillation permanent	50	15	11	11	9	4	1.2	1.8	1.1	1.4	1.0	0.6
Paroxysmal tachycardia	17	5	1	5	0	6	0.4	0.6	0.1	0.6	0.0	0.9
Cardiac arrhythmia only*	13	0	5	3	0	7	0.4	0.0	0.5	0.4	0.0	1.0
Cardiac neurosis	11	5	0	0	0	6	0.3	0.6	0.0	0.0	0.0	0.9
Recent rheumatic fever	13	6	4	0	0	3	0.3	0.7	0.4	0.0	0.0	0.4
Pericarditis	4	0	0	0	0	4	0.1	0.0	0.0	0.0	0.0	0.6
Heart disease due to chest deformity	10	2	0	5	0	3	0.2	0.2	0.0	0.6	0.0	0.4
Electrocardiographic abnormality only	32	6	5	5	3	13	0.8	0.7	0.5	0.6	0.3	1.9
Peripheral vascular disease	3	0	0	1	0	2	0.1	0.0	0.0	0.1	0.0	0.3
Nephritis (persistent albuminuria)	6	1	1	0	0	4	0.1	0.1	0.1	0.0	0.0	0.6
Hyperthyroidism	14	1	10	1	0	2	0.3	0.1	1.0	0.1	0.0	0.3

* Exclusive of paroxysmal tachycardia.

Report of Re-Examination of 4,994 Men Disqualified for General Military Service Because of Diagnosis of Cardiovascular Defects Robert L Levy (New York City) William D Stroud (Philadelphia) and Paul D White[5] (Boston) report that of 4 994 cardiovascular rejectees examined 863 were resubmitted as 1A and 4 131 had rejection as 4F confirmed (Table 1) Chicago yielded

TABLE 1.—RESULTS OF RE EXAMINATION BY SPECIAL BOARDS

	Total Five Cities	Boston	Chicago	New York City	Philadelphia	S n F
No. of cases						
Total examined	4 994	1 000	1 000	1 000	1 035	959
Resubmitted	863	188	38	192	171	274
Finally rejected	4 131	812	962	808	864	685
% of total cases examined						
Total exami ed	100 0	100 0	100 0	100 0	100 0	100.0
Resubmitted	17 3	18 8	3 8	19 2	16 5	28.6
Finally rejected	82 7	81.2	96.2	80 8	83 5	71 4

the lowest salvage (3 88 per cent) apparently because cardiovascular experts had been freely used in decisions about doubtful cases a procedure which might profitably be followed by other examining groups Causes for rejection are shown in Table 2 The principal one was rheumatic heart disease found in 2 476 men (50 per cent of the total and 59 9 per cent of the final 4F group) Mitral valvular disease without aortic valvular disease was diagnosed in 1 500 (750 with obvious stenosis) aortic valvular disease without apparent mitral valve involvement in 280 (72 aortic stenosis and 208 aortic regurgitation alone) and mitral and aortic valvular disease combined in 628 Auricular fibrillation complicating mitral stenosis was found in 24 cases Incidence of rheumatic heart disease varied from 70 3 per cent of rejectees in Chicago to 39 6 per cent in San Francisco

Hypertension was found in 1 059 cases (25 6 per cent of 4F cases and 21 per cent of total series) the majority

(5) J A. M A. 123 937 944 Dec. 11 1029 1035 Dec 18 1943

particular interest which remain unsolved and should be the focus of follow up study (1) interpretation of apical systolic murmurs (may they if very slight or even slight in absence of any other abnormal or doubtful finding be considered inadequate reason for rejection?) (2) upper limits of normal blood pressure (may the systolic pressure in very nervous young men be set perhaps as high as 160 mm or more provided diastolic pressure does not exceed 90 mm?) (3) limits of normal pulse rate at rest (may there not be a wider range say 40–120 per minute than that actually given in current criteria?) (4) heart size which also varies widely especially according to body build (5) electrocardiogram of which the wide range of normal has not been explored adequately (6) neurocirculatory asthenia difficult to diagnose when mild but probably rejectable even when slight unless there is obvious correctable cause (7) recent rheumatic fever a hazard even when the heart seems perfectly normal and (8) exercise tests the usefulness of which in cardiovascular examination for military service is questionable

Follow up of men reclassified as 1A and especially of doubtful borderline cases in the final 4F group should in future years aid in solving some remaining problems in cardiovascular diagnosis Wisdom of extending these re examinations for the sake of salvage alone is doubtful but applications of lessons learned should be helpful in future examinations

Significance of Gastro Intestinal Tract Abnormalities as Related to Management of Cardiac Disorders Clarence F G Brown and Ralph E Dolkart (Northwestern Univ) emphasize the inter relationship of reflex phenomena involving the cardiovascular and gastro-intestinal systems

Willius and Fitzpatrick 20 years ago reported that 39 per cent of patients with chronic gallbladder disease had associated changes of the cardiovascular system coronary artery sclerosis being the most common More recently Ravdin and his co-workers have recommended cholecys

(6) M Cl n N rth America 28 107 111 January 1944

showed elevation of both systolic and diastolic levels incidence varied little with geography but was relatively more common in the fourth than in the third decade Neurocirculatory asthenia was present in 204 cases with Negroes rarely affected Incidence varied from 8 per cent in Boston to 1 1 per cent in Chicago There were 189 cases of sinus tachycardia with numbers varying from 75 in Chicago to 8 in Philadelphia Congenital heart disease was found in 183 cases the commonest abnormality being ventricular septal defect (Roger s disease) in over a third Other congenital defects were patent ductus arteriosus pulmonary stenosis coarctation of the aorta auricular septal defect and subaortic stenosis City incidence varied from 63 cases in San Francisco to 18 cases in Philadelphia

Other causes for rejection included cardiac enlargement alone determined by roentgen examination in 76 cases arrhythmia in 32 electrocardiographic abnormalities alone in 32 cardiovascular syphilis in 17 thyrotoxicosis in 14 recent rheumatic fever in 13 cardiac strain from chest deformities in 10 coronary heart disease in 6 pericarditis in 4 and peripheral vascular defects in 3 Unspecified heart disease was diagnosed in 113

History of rheumatic fever was obtained in slightly over a fourth of those with rheumatic heart disease (28 8 per cent in four cities) and in nearly half of those in Boston and New York City History of chorea was rare

There were 386 Negroes among 4 035 men examined in four cities and a few Chinese and Filipinos There was a high rejection rate for Negroes (88 per cent) and a very high rejection rate for Chinese and Filipinos (100 per cent) Nine of 15 cases of aortic syphilis were among Negroes and hypertension was also more frequent in Negroes (38 5 per cent of final 4F cases compared to 23 1 per cent for white men) Rheumatic heart disease was evenly represented but neurocirculatory asthenia was much less in Negroes (0 9 compared to 5 5 per cent)

Tentative opinions are expressed about problems of

accentuates the frequency or degree of coronary artery spasm Treatment of hiatus hernia is either surgical or palliative Small frequent feedings careful maintenance of an upright posture during and considerably after eating and use of antispasmodics are indicated

Irritable bowel syndrome or nervous indigestion is one of the commonest gastro-intestinal tract abnormalities Almost any intra abdominal viscus may initiate reflexes which may affect the coronary circulation heart rate or rhythm It is well established that actual torsion or simple tension from any cause which twists or pulls a viscus sets up visceral reflexes which affect the entire circulatory system

Among the abdominal organs those classed as hollow viscera are the most frequent source of coronary embar rassment Emptying a distended bladder frequently re lieve dull precordial discomfort With a spastic bowel chest pain is often relieved by redistribution of gases or by a bowel movement with free expulsion of gas and re sultant lowering of intraluminal pressure All of these phenomena are increased by presence of organic changes in the gut wall With diverticulosis increased production of reflex stimulation may result when there is mechanical embarrassment in one or more of the diverticula which is further increased when actual diverticulitis and con comitant colon spasm exist

Modern Management of Injuries of the Heart. Hugh Barber states that accidents likely to injure the heart directly are crushing injuries of the thorax a blow over the chest and a fall from a height In the young and elas tic chest the heart may be damaged without fracture of thoracic bones The only strains worthy of consideration are intense efforts with chest fixed and glottis closed

Auricular fibrillation may follow intense strain in a previously normal heart If mitral stenosis or myocardial degeneration is present a comparatively slight effort may precipitate this arrhythmia Auricular fibrillation after a

(7) M P 211 164 166 M 1 1944

tectomy in patients with angina and diseased gallbladders Although Maisel and Alvarez reported that there is no proof that biliary tract disease has any direct influence in the production of heart disease the authors believe the clinical problem does not revolve around presence or absence of such a relationship Rather if presence of gall bladder disease acts as a reflex trigger mechanism through which the frequency of anginal attacks is increased removal of the associated abnormality the gallbladder is a constructive step in therapy Studies indicate that the coronary arteries are dilated by responses of the sympathetic system to adrenalin and constricted by the vagus It is probably through mediation with such reflex connections that gallbladder abnormalities alter the course of individuals with coronary artery disease

Accordingly careful search for gallbladder disease should be made in individuals who manifest food intolerances have associated stomach or bowel distress as indicated by gaseous distention after meals or upper right quadrant distress and evidence of coronary artery disease. Cholecystectomy in properly selected risks is definitely indicated and poor surgical risks should be managed with a view toward minimizing the reflex stimuli arising from the gallbladder

Hiatus hernia also enters into the inter relationship of cardiac and gastro-intestinal systems Not infrequently substernal pain radiating to the shoulder may be a presenting symptom of hiatus hernia and is commonly misinterpreted as of coronary artery origin Exertional dyspnea may be present but may result from reduction of vital capacity owing to presence of a large portion of the stomach in the chest Other cardiac symptoms may be the result of rotation or displacement of the heart or increased intra abdominal pressure from below The foregoing indicate the mechanical aspects of hiatus hernia which may mimic heart disease Both conditions may occur together and in such instances there is doubtless a reflex trigger mechanism as in gallbladder disease which

There has been considerable controversy about primary cardiac overstrain Occasionally after intense effort with chest fixed and glottis closed there is history of distress with dyspnea and perhaps a restless night It is difficult to dismiss this as neurosis but there are no physical bases for diagnois of heart disability If following strain there are dyspnea on exertion precordial discomfort with palpitation and perhaps some premature contractions a full investigation is essential including radiologic examinations to demonstrate absence of structural disease Persisting functional incapacity of the heart whether it appears to follow direct violence or an alleged strain requires all the encouragement the patient s physician can provide

Carotid Sinus Syndrome Since 1933 when Weiss and Baker reported 15 cases of an abnormally sensitive carotid sinus resulting in attacks of syncope and convulsions numerous cases of this type have been recorded but the phenomenon is not always borne in mind The vagus nerve the vasomotor depressor nerves and the central motor pathways may be called into play individually or collectively and the resultant clinical entity will depend on predominance of any particular pathway The three types of syndromes recognized are vagal characterized by cardiac slowing and asystole followed by syncope and a convulsion depressor marked by severe and often alarming fall in blood pressure and central in which no observable changes in blood pressure or heart rate occur to explain the syncope or convulsion Commonly the entity occurs in mixed form and then it is usually classified according to the most predominant finding

S L Zimmerman reports six cases observed at the U S Veterans Administration Facility Columbia S C Five were vagal the sixth was of the depressor type with associated low basal metabolic rate Medical treatment afforded some relief in four cases in one the patient was not admitted for treatment and another patient showed no response to atropine therapy The presence of

(9) J L b & Cl n Med 28 1548 1555 O tober 1943

crushing injury of the chest suggests a seriously injured heart for which long rest is indicated In normal hearts rhythm may be restored by quinidine Valvular or myocardial disease must be controlled by digitalis

An unusually slow rate after a blow over the chest is fairly common probably due to simple sinus bradycardia which will disappear in a few days without significant symptoms However it may be due to heart block so electrocardiography is indicated Extrasystoles are common after injury but their significance must be assessed in relation to other findings In the rare event of sudden death following a blow with no evidence of heart lesion *post mortem* a reasonable deduction is that injury set up ventricular fibrillation

Angina of effort the result of accident may appear after activity has been resumed after rest occasioned by other injury Prognosis apparently depends on original state of the heart and coronary arteries Sometimes angina persists but a good prognosis is justified Coronary thrombosis is rare after injury

Symptoms of myocardial contusion are distress of the accident and development of dyspnea precordial pain or discomfort and faintness some hours later Symptoms may be masked by associated thoracic or lung injuries a full investigation may show temporary electrocardiographic changes but prognosis for eventual recovery is good If a large hemopericardium develops the signs are of heart tamponade or compression of the heart The clinical picture of heart tamponade is especially important in case of a stab wound of the chest because it suggests a wound of the heart muscle which may be successfully sutured Traumatic pericarditis is an indication for surgical drainage

Persistent functional incapacity of the heart with symptoms simulating those of the senile heart with myocardial weakness may develop following some chest injuries but emphysema pneumoconiosis or other explanation of dyspnea must be excluded

disease. In the much rarer type the circulation abnormally diminishes when the patient assumes the erect position

Many weakened patients cannot stand without involuntary muscular movements of the lower extremities Such movements are always called forth in persons subject to fainting before they collapse and they seem designed to support the circulation Their presence is regarded as evidence of the inadequacy of the vasomotor and other circulatory responses to maintain blood pressure

Most patients with symptoms referable to their circulation without detected organic disease the group often diagnosed as having neurocirculatory asthenia show in co ordination of the circulation Frequency of such in coordination in many disease conditions is suggested as the *reason for the widespread occurrence of symptoms these* patients exhibit such as undue breathlessness on exertion faintness and dizziness

Analysis of Shock. Virgil H Moon[*] (Jefferson Med College) emphasizes the confusion that arises from the fact that three unrelated mechanisms may cause clinical signs of shock following injuries primary or neurogenic shock effects of hemorrhage and delayed or secondary shock. These may operate singly or in combination Traumatic shock is not a disease but a syndrome representing the summative effects of the aforementioned conditions Each causes low arterial pressure, hence they cannot be distinguished by that criterion

Physiologic disturbances which accompany secondary shock are not the same as those of hemorrhage (see Table) Simple uncomplicated hemorrhages apparently will not produce the shock syndrome but hemorrhage when present is a highly important contributory factor A person in whom secondary shock is developing may not withstand the loss of an amount of blood which would be insignificant in an otherwise normal person Loss of capillary s and abnormal permeability of endothelium are im

* B M J 1 773 779 J e 10 1944

the syndrome was easily established in all six cases In two the precipitating factor was an abnormal or sudden movement of the head a third patient learned that he could avoid an attack by holding his head between his hands

Treatment is usually medical unless attacks are frequent and incapacitating Worry and fatigue should be *minimized* The vagal type often responds to atropine sulfate 1/150 gr three to four times daily sometimes supplemented with ephedrine adrenalin benzedrine or paredrine The depressor type may be relieved with any of the sympathomimetic drugs

[The editor recently saw a patient with this syndrome cured by the *removal of a suture needle from the right tonsillar fossa*, left there many years before during a tonsillectomy —Ed]

Clinical Studies on In co-ordination of the Circulation As Determined by Response to Arising are reported by Isaac Starr[1] (Univ of Pennsylvania Hosp) Circulatory adaptation can be studied by observing changes in cardiac *output and blood pressure which follow change of* position Response of the circulation when the subject arose as determined by the ballistocardiograph was used as a test of its co ordination *i e of ability to adapt the cardiac* output to the needs of the moment Normal standards for circulatory co ordination were determined by a statistical analysis of the results of 120 tests made on *75 healthy* young adults before and after rising while abnormalities were studied by about 200 tests on 150 ambulatory patients

In healthy persons the physiologic adjustment necessitated by assuming the erect position is largely accomplished by the vasomotor mechanism and the cardiac output changes but little In many sick persons the cir*culation changes much more* and the abnormality may be in either direction In the commoner type the circulation is unduly increased on arising as if the vasomotor responses *were ins cient to support the blood pressure* unaided This is found frequently in many types of

(1) J Clin Invest, 22 813 826 November 1943

respond more readily to treatment than do those with advanced secondary shock Observations on concentration of the blood and consideration of time elapsed since injury are valuable in determining which mechanism is the major factor causing circulatory deficiency Loss of blood volume is an outstanding feature after hemorrhages and in secondary shock After serious hemorrhages transfusions of whole blood provide the ideal remedy In shock accompanied by hemoconcentration the patient does not lack erythrocytes but needs fluid to restore the blood to normal composition and volume hence the ideal replacement fluid is human plasma or serum in normal or isotonic concentration However the same amount of plasma concentrated to one half or even one fifth its *original volume is far more effective in counteracting both* low blood volume and deranged equilibrium of fluids which are prominent factors in the mechanism by which shock develops

Early recognition and treatment are important if favorable results are to be achieved Treatment must anticipate the complicated interplay of agencies whose combined effects culminate in the syndrome of shock It must be administered before failing circulation and associated anoxia have produced irreversible changes in tissues whose functions are vital

Heart in Pregnancy Prognostic Aspects are discussed by William A Sodeman and Edward L King[3] (Tulane Univ) Use in obstetric cardiacs of the New York Heart Association classification has met with widespread enthusiasm Generally the rule holds that patients in class I will give little or no trouble those in class II probably will not those in class III may present a serious problem and those in class IV present not only difficulties in management but also a high mortality In applying these rules to the pregnant woman it must be recognized that certain symptoms used in classification of cardiac patients in general may arise in normal pregnant women and

(3) South. M. J 37 235 239 Ap il 1944

portant factors in secondary shock but have not been shown to play a part either in primary shock or in the effects of hemorrhage Abnormal permeability disturbs the mechanism of fluid balance leading to edema of viscera and hemoconcentration Serious derangement of renal

CONTRASTED FEATURES

ITEMS	SHOCK	HEMORRHAGE
Endothelium	*Permeable to colloids*	*Impermeable*
Flow of lymph	Increased	Decreased
Tissue fluid	Increased	Decreased
Fluid balance	Disturbed	Undisturbed
Absorption	Impaired	Unimpaired
Vomiting	Persistent	No vomiting
Diarrhea	Frequent	Absent
Saline, intravenous	Ineffective	Often effective
Renal		
Excretion	Deficient	Unimpaired
Urine	Concentrated, low volume, albumin, erythrocytes bile debris	No characteristic changes
Blood		
Coagulation time	Lengthened	Shortened
Concentration	Increased	Decreased
Nonprotein nitrogen	Increased	Decreased
Potassium	Increased	Terminal increase
Plasma chlorides	Decreased	Increased
Necropsy findings		
Edema of soft tissues	Characteristic	None
Serous effusions	Present	Absent
Capillovenous congestion	Characteristic	Absent
Petechiae	Characteristic	Absent
Visceral ischemia	Absent	Present
Organ weight	Increased	Decreased
Gastro-intestinal tract	Dilated, atonic	Contracted
Parenchymal necroses	Present	Absent

function accompanies secondary shock This is seen after injuries and burns with intestinal obstruction mesenteric thrombosis metabolic intoxications anaphylaxis transfusion reactions severe infections and from effects of various poisons.

Clinical management of shock requires recognition of the causative mechanism Patients with primary or hemorrhagic shock unless accompanied by extensive trauma

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Plasma chlorides	Decreased	Increased
Necropsy findings		
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function accompanies secondary shock This is seen after injuries and burns with intestinal obstruction mesenteric thrombosis metabolic intoxications anaphylaxis transfusion reactions severe infections and from effects of various poisons

Clinical management of shock requires recognition of the causative mechanism Patients with primary or hemorrhagic shock unless accompanied by extensive trauma

vertigo syncope anginal pain and sudden death appearing with little warning Acute rheumatic fever is rare in *pregnancy Carr found only* 8 instances in 1 061 consecutive cases of chronic rheumatic heart disease in pregnancy Sudden changes in blood pressure often develop in pregnancy and may be accompanied by signs of heart failure The patient with hypertensive disease demands close careful frequent examinations to make possible adequate prognostic and therapeutic plans which cannot be based solely on the functional classification Congenital lesions account for 1 5-2 5 per cent of cardiac disease in pregnancy lesions with arteriovenous shunts and coarctation of the aorta add to pregnancy hazards which are unpredictable by the functional classification Marked aortic regurgitation offers a serious prognosis and obviously the insult of pregnancy is to be avoided

Despite the fact that the patient may be well compensated and fall in class I history of previous congestive heart failure indicates impaired cardiac reserve and possibility of recurrence In one group 75 per cent with past history of heart failure developed heart failure again in pregnancy whereas among those with no previous decompensation failure developed in only 15 per cent Pregnancy does not seem to be important as a cause of subacute bacterial endocarditis nor does it confer immunity or hasten the disease Prognosis for the mother is hopeless but for the fetus is good Therapeutic abortion is not indicated but the mother is carried to term or to the period of viability cesarean section is indicated on the moribund patient Tuberculosis nephritis and diabetes affect cardiac reserve and must be considered in prognosis

Etiology Diagnosis and Treatment of Acute Dilatation of the Heart. A Graham Asher states that clinical cases of acute dilatation present various mixtures of tonogenic and myogenic types and treatment and prognosis rest on the predominating factors Acute hypertension vasomotor disorders and anoxia lead to tonogenic dilatation Treat

(4) K C ty M J pp 15 18 M J 1944

evaluation must be made in terms of the normal pregnant woman of similar type and stage of pregnancy The cardiac state in pregnancy is not static with progress of pregnancy or of heart disease and changes in environmental factors a patient may need reclassification Common cause of cardiac strain such as infection exercise sudden rises in blood pressure psychic trauma hemorrhage shock coitus alcoholism dietary excesses malnutrition anemia and arrhythmias associated with rapid heart action become doubly important when added to the strain of pregnancy A prime function of prenatal care is to forewarn the patient of these because they are largely removable or preventable

Such factors however do not explain all discrepancies found in classifying heart disease in pregnant women Other aspects in the individual case enter into the evaluation including age auricular fibrillation marked cardiac enlargement aortic stenosis rheumatic activity hypertension certain types of congenital heart disease syphilitic aortic regurgitation previous congestive heart failure bacterial endocarditis and important complicating disease Age at which the patient becomes pregnant has a direct bearing on possible development of congestive failure even though the functional classification at the outset is class I In one series of patients only 16 1 per cent of those under 30 developed signs of heart failure while this increased to 43 6 per cent in patients over 30 Auricular fibrillation adds an increased hazard and may be considered an adequate contraindication to pregnancy However if the woman knows the risk involved and has real desire for a child intensive treatment may make possible continuation of pregnancy with adequate control of heart rate by digitalization and a rigid program of rest Marked cardiac enlargement reflects severe cardiac strain and the additional strain of pregnancy increases the insult in a condition with an already grave prognosis Patients may withstand the effects of aortic stenosis for many years but in some cases there may be dramatic symptoms including

ly but moderately to relieve pain Stimulation should be both central myocardial and peripheral vascular with caf feine sodiobenzoate or coramine Hypodermic doses of adrenal cortex extract 4–8 cc in two doses have re stored blood pressure Careful use of small doses of adren alin and pituitrin is sometimes required for residual vaso motor paralysis Oxygen in large amounts reduces the dis tress and anoxia and should always be used

Acute Ventricular Failure Harry Evan Rollings (New Orleans) states that myocardial failure may be rapid though usually it is slow and insidious Unlike anginal failure it is never instantaneous Clinically discernible cardiac enlargement always precedes it and serves as a valuable differential point in that edema and dyspnea oc curring with a heart of normal size must be ascribed to causes other than heart muscle failure The heart muscle may fail first on the left side or it may begin on the right more rarely it occurs on both sides simultaneously In analysis of etiologic factors in 1 000 cases Poyer Leath and White found hypertension with or without coronary heart disease in 47 per cent rheumatic heart disease in 26 per cent uncomplicated coronary heart disease (ex cept by myocardial infarction) in 16 per cent No other factor was responsible for as much as 5 per cent incidence Males outnumbered females about 2 1 Precipitating fac tors which superimposed on these underlying causes pro duced heart failure were auricular fibrillation 14 per cent coronary thrombo is 13 per cent respiratory infec *tions 11 per cent rheumatic fever 7 per cent* pulmonary infarction 3 per cent In 38 per cent onset was gradual with ill defined or no precipitating factor and in 5 per cent onset was sudden but precipitating factor was un known Prognosis depended more on the exciting than on underlying causes or age A poor prognosis was always associated with marked cardiac enlargement Hyperten sion when present increased incidence of decompensation in patients with myocardial infarction

(5) N w O l M & S J 96 446 455 Ap l 1944

ment directed to these causes may be rapidly effective. Myocarditis arteriosclerosis toxemias and effort under congestive failure lead to myogenic dilatation treatment must be symptomatic and supportive with attack on pathogenesis less rapidly effective With acute cor pulmonale and valvular defects such as aortic or mitral stenosis both forms of dilatation occur with acute precipitating strain cyanosis and myocardial damage determining the proportions

Acute dilatation is a real emergency and diagnosis must be made early and at the bedside to be life saving or even to relieve the great distress Onset is abrupt or rapidly progressive with marked precordial pain or oppression angor animi air hunger collapse and shock Symptoms and signs parallel those of acute myocarditis Marked pallor is more frequent than marked cyanosis Tachycardia and palpitation are the rule occasionally abnormal or terminal bradycardia. Favorable signs of improvement are lessening of distress slowed respiratory and pulse rates and improvement of heart tones and murmur usually with rising blood pressure

Physical signs of enlargement may be slight On percussion extension of the right border to more than 1 cm to the right of the right sternal border and of the left border to beyond the midclavicular line is a presumptive sign of dilatation or pericardial effusion Dilatation of the right heart associated with hypertrophy gives Mackenzies sign—diffuse systolic retraction of interspaces along the lower sternum An apex beat displaced only outward indicates dilatation of the right ventricle an apical impulse displaced both outward and downward suggests dilatation of the left ventricle Dilatation of the right auricle causes dulness to the right of the lower right sternum that of the left auricle leads to filling in of an area of dulness at the cardiac waist or the upper concave area above the left ventricle

Treatment is that of an acute cardiac emergency with pain anoxia and failure Morphine should be used prompt

decompensating heart It helps slow heart rate also through depression of sino auricular and auriculoventricular nodes Dosage must be carefully individualized and severity of the patient s condition is a guide to the urgency of speed of digitalization in extremely severe conditions it may be administered intravenously Oxygen is being widely used and may furnish dramatic relief from restlessness and tachypnea Opinions differ regarding use of diuretics They cannot be expected to remove large collections of fluid from pleural or peritoneal spaces For this purpose paracentesis is the proper procedure often affording relief by improving respiration Diuresis often follows paracentesis resulting in diminution of peripheral edema Mercurial and xanthine diuretics are effective in many cases of heart failure Venesection is life saving in acute pulmonary edema blood should be removed rapidly since minute count Even in ordinary congestive heart failure removal of a large amount of blood may give the failing heart just the re pite needed to lead to recovery instead of progressive failure Adrenalin and other vasopressor drugs have no place in treatment except in case of ventricular standstill when it may be boldly injected directly into the heart chamber Use of caffeine coramine and cardiazol is not indicated unless respiratory stimulation is needed Squill glucoside or urginin is sometimes effective in rare cases of intolerance to digitalis

Care of Patient with Chronic Heart Disease is described by Fugene A Stead Jr and James V Warren (Emory Univ) As long as the heart is able to put out blood required for the daily routine failure does not occur When it is not able to maintain normal circulation symptoms of failure develop If the patient is put at rest these will quickly disappear without medication because the heart is still capable of maintaining normal circulation at rest Thus the patient can be compensated for a long time by reducing his activity and thus reducing the amount of

( ) M Cl n N th Am 28 381 387 M h 1944

In evaluating the individual case one must assemble all precipitating and underlying factors presented weigh their importance in their association with actual structural and organic changes and realize the prognostic significance of the exciting cause Evaluation of breathlessness is important because it antedates appearance of physical signs of heart disease other than enlargement

Hypertrophy and dilatation are the natural reaction of a heart in its attempt to compensate for stresses put on it by constant excess mechanical burden For a time the attempt at compensation is successful and the work of the heart continues so the patient is free from symptom and thus ignorant of impending danger Finally compensation becomes inadequate and breathlessness appears on exertion Soon after edema of varying degrees is seen in dependent parts of the body then the failing heart is subjected to some added stress perhaps a respiratory infection prolonged tachycardia or overexertion and a sudden attack of pulmonary edema may be precipitated Such a patient is usually seen sitting erect fighting for breath terrorized because of a feeling of suffocation and often further encumbered by a hacking cough Perspiration is profuse superficial veins are engorged and distended With increasing severity of pulmonary edema frothy blood tinged sputum may appear Immediate attention is essential if life is to be preserved Rest sedation digitalis oxygen and diuretics are the most potent weapons in combating acute cardiac emergencies

In an acute attack morphine should be administered other sedatives may be used when the condition is semichronic Digitalis is the most important weapon in control of congestive heart disease its most significant effect is lengthening of the refractory period and depressing or slowing auriculoventricular conduction Control of tachycardia and irregular rhythm of auricular fibrillation depends on this action Direct effect on the myocardium also is important it increases tone of the heart muscle and contractility of muscle fibers thus aiding the dilated

ventricles When the heart is poisoned with potassium chloride the ventricles dilate the venous pressure rises in the left and right auricles and there is a tendency toward a decrease in ventricular output

In one experiment in which diastolic volume and oxygen consumption were kept constant there were a decrease in the mechanical efficiency of the heart a tendency toward a decrease in minute output of the ventricles as well as the mean blood pressure and a rise of venous pressure in the left and right auricles

Digilanid C (cedilanid) increases the mechanical efficiency of the heart provided the heart failure has not been allowed to go too far It increases cardiac output decreases ventricular dilatation and decreases venous pressures

Constrictive Pericarditis Classic Type with Pericardiectomy Charles K Friedberg[8] (New York City) reports a case in a man 38 as representative of a group of cases of intractable and otherwise irremediable congestive heart failure due to constrictive pericarditis which is amenable to surgical treatment Possibility of an excellent therapeutic result with operation presents an important diagnostic challenge in distinguishing constrictive pericarditis from congestive heart failure due to various intrinsic cardiac and valvular diseases from cirrhosis of the liver and from other clinical conditions Segregation of constrictive pericarditis as an entity is impeded by its uncertain etiology absence of a characteristic clinical diagnostic test or of a specific pathologic lesion and even by some disagreement as to its clinical features

The typical case is characterized by ascites pleural effusions venous engorgement and a high venous pressure which persist despite prolonged and rigid medical treatment for heart failure The heart is normal or small or at least not significantly enlarged systolic blood pressure is normal or low pulse pressure is diminished and cardiac pulsations are hardly noticeable

At operation the pericardium is thickened and avascu

(8) J Mt S H p 10 717 7 I J F b 1944

blood pumped per day In time regardless of limitation of activity cardiac output becomes inadequate and symptoms reappear By proper use of digitalis the heart can be strengthened again with disappearance of symptoms. After a time cardiac output is further decreased, and despite digitalis and limited activity symptoms of congestive failure are present The resting cardiac output is low and salt and water retention will occur even at rest Because many symptoms of congestive failure result from interference in function of the lungs and other organs due to excessive retention of salt and water the patient can be kept comfortable even with a moderate decrease in cardiac output if such retention is kept minimal by use of diuretics and limitation of dietary intake of sodium In time salt and water retention occurs despite constant therapy and the patient becomes waterlogged and dies

Thus the patient with congestive failure can be helped (1) by rest so that body requirements for blood are less *and daily heart output can be decreased without interfering* with body economy (2) by strengthening the failing heart with digitalis to maintain an output compatible with necessary activity and (3) by eliminating salt and water which tend to be retained when cardiac output becomes insufficient to support the daily routine of living In practice these measures are combined to fit the needs of the individual patient

A Physiologic Definition of Acute Congestive Heart Muscle Failure is presented by George Fahr and Martin S Buehler (Univ of Minnesota) based on animal experiments These proved that decreased mechanical efficiency is the basic factor in acute congestive heart failure

Cardinal features of spontaneous heart failure or that produced by chloroform chloral hydrate alcohol and diphtheria toxin are (1) a decrease in mechanical efficiency of the heart (2) dilatation of the ventricles (3) rise of venous pressure in left and right auricles and (4) a tendency toward a decrease in minute output of the

(7) Am Heart J 25 211 41 February 1943

tem which they either connected with or attributed to a previous chest injury Among the first group of patients with relatively mild nonpenetrating chest injuries 15 had cardiac damage (about 7 per cent) thought to be due to the injury directly or aggravated by it Thirteen of the 36 patients in the second group which represented more serious injuries had heart conditions thought to be caused or aggravated by the accident

Nearly all patients in both groups were at the age when coronary disease and hypertension are most prevalent Only three were in the early part of the fourth decade The severity of chest trauma and chances of cardiac damage do not necessarily correspond There were many patients with severe chest injury and bilateral rib fracture of as many as 11 and 13 ribs without cardiac involvement It is apparently the degree of elasticity of the chest wall and the type of blow which determine the chances of cardiac injury by anteroposterior compression It is also conceivable that in cases in which fracture of ribs does occur the force of the impact is broken or diminished thereby causing less or no damage to the substratum

In many instances it is difficult to decide whether or not the cardiac disability is related to the trauma Many pa *tients are prone to attribute any and all ills to a previous* injury particularly when symptoms emanate from or near the site of injury The tendency for some injured to exaggerate symptoms for purposes of compensation should not be overlooked

Symptoms Referable to Digestive Organs Resulting from Diseases of Abdominal Blood Vessels are reviewed by I W Held (Beth Israel Hosp New York City) These may be due to arteriosclerosis of the abdominal aorta and gastric and intestinal vessels spasm of intestinal vessels or thrombosis of mesenteric vessels abdominal aorta or portal vein Related vascular conditions to be con sidered are angioneurotic edema and periarteritis nodosa Many symptoms of these conditions simulate diseases of

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lar and may be calcified its resection is followed by sharply increased pulsations bulging of the heart through the pericardial defect and elevation of systolic and pulse pressure Postoperatively adequate decortication is followed by progressive clinical improvement but return of venous pressure to normal may be delayed many months

Problems in Diagnosis of Heart Disease Joseph C Edwards (St Louis) stresses particularly the differential diagnosis of functional heart conditions and evaluates various signs and symptoms such as murmurs pulse irregularity blood pressure fluctuations pain and neurocirculatory asthenia as to their significance in this differentiation The distinction between functional and progressive organic heart disease often is difficult to make A physician should not hesitate however to express the opinion that the heart is normal if careful examination justifies it Failure of the physician to recognize the condition as functional may condemn the patient to a life of inactivity or invalidism When there is no cardiac lesion or one not sufficient to cause the symptoms complained of the physician should say so emphatically When doubt exists he will render his patient a service by consulting a cardiologist rather than to allow the patient to live in uncertainty and fear and perhaps progress to a cardiac neurosis It is just as serious to put a patient to bed for weeks for functional pain because of an improperly interpreted electrocardiogram in the absence of myocardial infarction

Traumatic Heart Disease Clinical Study of 250 Cases of Nonpenetrating Chest Injuries and Their Relation to Cardiac Disability H Arenberg[1] (New York City) divides this series of patients into two groups The first consisting of 214 patients sought medical aid because of injury to the chest and the time interval between accident and observation varied from several hours to as much as 10 weeks The second group of 36 patients complained of symptoms referable to the cardiovascular sys

(9) J M sou M A 40 314 318 October 1943
(1) Ann. Int Med 19 326 346 August 1943

Blood pressure was 110/80 pulse 100 Past medical records showed that the heart had previously been normal A chest roentgenogram showed fulness in the region of the pulmonary conus with some increase in root shadows on both sides thought due to passive congestion The heart did not appear to have a mitral lesion it occupied 45 5 per cent of the transverse diameter of the thoracic cavity Electrocardiogram showed a rate of 110 with normal sinus mechanism P R interval 0 16 Q S interval 0 06 and QRS T interval 0 28

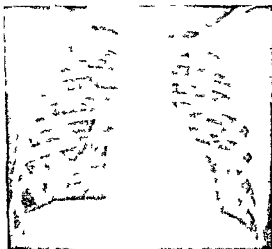


Fig 88—F t dm x d y ft de t.

QRS groups in the classic leads were low II and III showed large Q waves This was felt compatible with a congenital detect The patient was discharged seven days after the accident

Seventeen days after the accident the murmur was shriller and more musical Sedimentation rate was normal The electrocardiogram showed remarkable change primarily in T waves indicating diffuse myocardial damage mainly in the posterior wall Besides a Q in II and III there were an elevated S T in IV and deeply inverted T waves in II III and IV Readmission was advised with a provisional diagnosis of contusion to the myocardium and rupture of the interventricular septum During the interval at home the boy had

the gastro intestinal tract with the primary cause confined to the blood vessels Arteriosclerotic changes in the abdominal aorta can even simulate carcinoma of the stomach

Treatment of mesenteric thrombosis and many of these conditions if not caused by an underlying fatal disease is primarily surgical Only rarely does canalization take place with spontaneous recovery A ruptured abdominal aorta is not amenable to treatment and frequently is not diagnosed correctly Conditions which can be influenced by medical treatment include gastric ulcer due to sclerotic changes in small arteries of the stomach vague digestive symptoms due to sclerotic changes in vessels of digestive organs other than the stomach dyspragia intermittens angiosclerotica intestinalis angioneurotic edema and periarteritis nodosa in the rare cases affecting the gallbladder or appendix without systemic involvement

As degenerative changes in the blood vessels occur there is first a period of angioneurosis during which *symptoms are psychic and reversible In the period* of transition they become psychosomatic Finally the digestive organs are so deranged by arteriosclerotic changes in abdominal blood vessels that the symptoms are no longer amenable to treatment In the angioneurotic or presclerotic state it is important to remember that these are functional disturbances with a potential organic basis Patients must be treated both as angioneurotics and as requiring preventive measures They are subject to development of peptic ulcer which calls for a special preventive regimen

Traumatic Cardiac Injury in a Child with Probable Rupture of Interventricular Septum is reported by Edwin D Bayrd and Stanley Gibson (St Lukes Hosp Chicago)

Boy 11 was hit by an automobile and lost consciousness for a short time complaints on admission were headache and severe pain in the left upper chest quadrant The heart exhibited a marked systolic thrill producing actual vibration of the chest wall and a harsh murmur limited to systole over the whole precordium Heart size was normal to percussion

(8) J Pediat 4 138 147 February 1944

grams (Fig 90) showed progressive changes back toward normal abrupt in the fourth lead gradual in the second and only slight in the third with a marked Q wave and inverted T wave continuing to mark the site of maximum injury The T wave in IV reverted to the upright position on the thirty third day A stethographic tracing 22 days after the accident demonstrated a long murmur filling systole with no diastolic murmur but a third heart sound in the apical lead.

The patient was discharged 29 days after the second ad

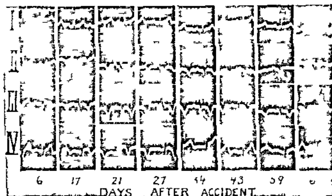


Fig 90 —F t ght elect oca d og ms.

mission 47 days after the accid nt feeling well He had no pain in the chest during the last three weeks of ho pitaliza tion Later examinations with electrocardiograms showed con tinuation of the healing process with a complete return to normal of the second lead and a less pronounced Q_3 T_3

In this case the diagnosis of recent heart trauma due to a nonpenetrating wound to the chest is firmly established on the basis of the patient s age history of injury lack of previous cardiac history appearance of a significant mur mur and thrill not present earlier and progressive changes in serial electrocardiograms indicating actual contusion of the muscle wall That the damage was not limited to the myocardium is established by sudden appearance of a marked systolic murmur and thrill Several possible causes of this murmur were considered rupture of the inter

been physically active but only slightly dyspneic had no substernal distress and complained only of a little sticky pain over the apex this was not related to exercise or relieved by rest but was most marked when he was tired

Examination revealed a diffuse apical impulse in the fourth and fifth interspaces about 6 cm from the midsternal line A thrill limited to systole was palpable over the entire precordium and to the right parasternal line and was maximal just left of the ensiform proce s in the fifth interspace The

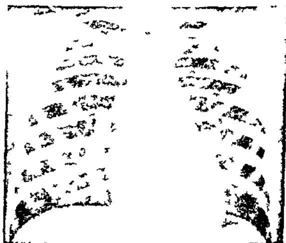


Fig 89 —\n ty th d y ft ac d nt.

left border of dulness was approximately 7 5 cm from the midsternal line about 1 25 cm left of the midclavicular line A musical very loud systolic murmur (like a rain crow) was heard over the entire chest anteriorly and posteriorly louder over the precordium and loudest left of the sternum in the fifth interspace It was not transmitted into the neck but was heard well in both axillae At the base over the pulmonic area the murmur was obliterated by a harsh rumbling rolling systolic murmur No diastolic murmurs were present M_1 was replaced by the murmur and M was faint. P was loud and snapping could be felt with the finger tips and was much greater than A First sounds at the ba e were replaced by the murmur Blood pressure was 95/68 pulse 100

Repeated chest roentgenograms showed no essential change in configuration (Figs 88 and 89) Repeated electrocardio

THE PERIPHERAL BLOOD VESSELS

Peripheral Vascular Diseases, with Special Reference to Those Seen in the Fighting Forces Treatment is discussed by F A R Stammers For diagnosis and prognosis and especially for selecting treatment the most important consideration is differentiation of symptoms due to arterial disease and to accompanying vasospasm Tests for vasospasm include effect of a warm environment heating the trunk fever and spinal anesthesia The commoner peripheral vascular diseases of the comparatively young are thrombo-angiitis obliterans Raynaud s disease hyperhidrosis scalenus anticus syndrome acrocyanosis frigida and vasospasm following poliomyelitis

There are many forms of treatment for these diseases varying from change of climate to intricate operations Change of climate at least during winter is of great benefit in Buerger s disease acrocyanosis frigida and poliomyelitis with vasospasm Occupations involving exposure to damp and cold or immersion of the hands in water are bad Warm covering for hands and feet should be provided Feet should be washed frequently and well dried and nails should be cut with great care avoiding injury to the nail folds or pulp Corns should be cut only by a chiropodist

For Buerger s disease in which symptoms are not relieved by these simple measures some form of pressure pulsator such as the pavex apparatus is most beneficial Contrast baths daily and gentle massage also are useful Injections to stimulate the vasodilators e g padutin or to produce mild pyrexia e g TAB vaccine are effective in some severe cases A weekly dose of TAB for six weeks sometimes gives prolonged ameliorization of symptoms

For the cervical rib syndrome operation is the only rational treatment Scalenectomy is the essential part of the procedure but when there is a definite cervical rib over which the radial plexus is stretched it must be re

(3) M P 11 308 313 M y 17 1944

auricular septum rupture of the right anterior sinus of Valsalva into the right ventricle rupture of the aortic valve traumatic pericarditis rupture of the mitral valve *rupture of the chordae tendineae rupture of papillary* muscles and rupture of the interventricular septum

Timing character and location of a murmur due to rupture of the auricular septum sinus of Valsalva or aortic value excludes these conditions since such lesions would produce basal diastolic murmurs Early abrupt onset of the murmur (present 1½ hour after accident) its character and *persistence* speak *strongly* against pericardial friction rub Electrocardiographic findings were not *typical of acute pericarditis* Shape of the heart *and its* constancy in roentgenograms did not indicate pericardial effusion which usually follows and there was no significant precordial pain at any time Mitral valve rupture is usually secondary to pre existing valvular disease and when it does occur respiratory distrēss is almost immediate and much more prominent than cardiac findings prognosis is poor and most patients succumb within a few hours to days Murmurs described in reported cases of *rupture of chordae tendineae or papillary muscles* differ considerably from those in this case

In 25 previously reported cases of acquired *defects of* the interventricular septum due to coronary disease no murmur was noted in 6 (5 reported between 1845 and 1906) in 19 there was loud rough shrill or harsh systolic murmur in 15 systolic thrill and in 2 soft diastolic murmur Most patients with acquired interventricular septal defect due to trauma died instantly one who lived long enough to be described had a systolic thrill and loud systolic murmur masking all heart sounds maximal at the apex Hence the authors feel that the heart injury in their patient was due to rupture of the interventricular septum *Such occurrences are rare and survival* is unique

Before concluding that a method of therapy has demonstrated its value various phases of spontaneous improvement must be recognized and evaluated Collateral circulation develops quickly after a major artery is occluded most ulcers tend to *heal spontaneously* and *cessation of* smoking changes to warm climates and elimination of psychic factors result in improvement these factors must be assessed in judging any specific treatment Rest should be judiciously prescribed When infection severe ulceration or gangrene is present rest should be fairly complete but it must be remembered that prolonged bed rest tends further to impair the circulation Patients with incipient or moderate vascular disease should obtain exercise to tolerance i e to the point of pain If a limb is kept elevated it becomes ischemic if it is lowered too far tissues become engorged and cyanotic Generally it is best to maintain a position so that the distal end of the limb is about 6 in below the heart level (usually the point where superficial veins just fill) Elimination of spasm producing *substances is perhaps the most important aspect of medical* treatment of peripheral vascular disease and should be rigidly enforced Although spasm of major vessels is not important in arteriosclerosis collateral vessels are usually not sclerotic and may be contracted Complete abstinence from smoking should be emphasized for every patient with impaired circulation Exposure to cold and emotional displays such as excitement fear rage anxiety etc should be avoided Sympathomimetic drugs such as epinephrine ephedrine and benzedrine should not be administered Value of vasodilating drugs singly or collectively in treatment of arteriosclerosis obliterans is limited Nonspecific protein therapy such as typhoid vaccine intravenously is probably the best single measure in treatment of Buerger s disease especially during active phases Physical methods of treatment include heat in various forms (sitz bath thermostatically controlled cradles whirlpool baths paraffin baths) gentle massage suction pressure (pavaex) intermittent venous occlusion postural exercises oscillating

moved or when a tight fibrous band replaces it this must be excised The man with bottle neck shoulders who has symptoms only when wearing a pack will not be helped by operation and must be assigned to duty not requiring wearing of a pack

When regulation of climate occupation clothing and hygiene has failed to benefit patients with Raynaud s disease acrocyanosis frigida poliomyelitis with vasospasm and hyperhidrosis preganglionic sympathectomy relieves and sometimes cures For the lower limbs a large majority are cured but relapse follows about 50 per cent of operations for the upper limbs Nevertheless when symptoms are severe or gangrene of fingers is threatened operation should be advised

The most serious peripheral vascular disease is thromboangiitis obliterans Young men in the early stages respond to surgery but older patients do not benefit sufficiently to justify it After experience in nearly 100 cases Stammers believes that operation for Buerger s disease is of no use in any patient over 35 As soon as this diagnosis is made in a man in service he should be discharged for it is a great liability to retain him

Peripheral Vascular Diseases are classified most simply as organic functional and combined organic and functional types A true organic vascular disturbance is rare there is almost always some degree of spasm superimposed on organic occlusion and organic changes are likely to occur following prolonged vasospasm Therefore most cases are properly classed in the third group Robert Schwartz (Pittsburgh) and Harry Warshawsky (White River Junction Vt) state that a definite etiologic diagnosis often is impossible it is more important to recognize that vascular impairment is present and to begin treatment promptly

Treatment has three main objectives to improve collateral circulation and relax spasm alleviate pain and remove nonviable parts at the optimal time and level

(4) M Bull. V t Adm n. 20 389 412 Ap 1 1944

are used as vasodilators The extremity should be wrapped in cotton to preserve its natural warmth with a heat cradle over the bed and temperature controlled not to exceed 95 F The extremity is placed in a slightly dependent position by elevating the head of the bed Room temperature should be approximately 90 F if possible Hot packs may be applied to uninvolved limbs to induce reflex vasodilation Short wave diathermy to the lumbar area or spinal anes thesia may be used for the same purpose Suction pressure therapy intermittent venous occlusion and the Sanders oscillating bed are also indicated in acute arterial occlu sions either individually or collectively If facilities are available embolectomy should be performed early

Mechanism and Treatment of Raynaud's Disease Psychosomatic Disturbance Isidor Mufson (Columbia Univ) believes that in Raynaud s disease a continuous flow of vasoconstrictor stimuli is maintained by a chronic psychosomatic disturbance These induce a partial angio spasm which becomes complete when the skin is exposed to cold Primary and complete obliteration of the lumen of minute vessels results from a compounding of two forces one emotional and the other physical Secondarily thrombi appear in these injured vessels and the local fault de velops *Cooling of the skin is the trigger mechanism which* renders complete the partial occlusion of minute vessels initiated and sustained by personality and social economic derangements This cyclic type of vasospasm can further induce a nonspecific endarteritis with secondary spasm and endovascular thrombi Additive effect of these leads to chronic anoxia of tissues with sequelae of ulcers and gangrene

Only a combination of therapeutic measures directed first to an improvement in mental hygiene and alleviation of social economic derangements and secondly to an in crease in collateral circulation will obtain a total cure in Raynaud s disease This method of treatment has enabled Mufson to bring relief to those in whom through co

(5) A I t Med 20 228-238 F bruary 1944

bed and mecholyl iontophoresis Extreme care must be exercised in application of heat to keep the temperature about 93–95 F Temperatures above 100 F produce excessive metabolic demands and may lead to severe ulceration or gangrene Baking with strong bulbs infra red lamps diathermy and ultraviolet rays is condemned for this reason

Every conservative measure should be used in treatment of peripheral vascular diseases before resorting to radical surgery because these patients are not good surgical risks Nerve block by direct infiltration of peripheral nerves with 1 per cent novocain relieves pain and improves local circulation but the effects are temporary Sympathetic ganglion block is used in treatment of acute thrombophlebitis for lower extremities the lumbar paravertebral route is used and for upper extremities the stellate ganglion is infiltrated Novocain is first used and if this is successful in relieving symptoms a more permanent effect may be secured by alcohol injection or sympathectomy Sympathectomy should be performed only if tests show an open collateral circulation Peripheral neurotomy has been used occasionally for relief of intractable pain Embolectomy in acute cases is of little or no value unless performed within a few hours Amputation is used as a last resort when irreversible gangrene is present or for diabetic patients who have spreading infection Site of amputation is vitally important for successful healing and amputation is best delayed until nature has demarcated the area involved localized infection and attempted autoamputation

In managing cases of acute thrombosis or embolism one should not (1) delay treatment more than two or three hours (2) elevate the extremity or (3) subject the limb to heat which exceeds body temperature more than a few degrees Heparin infusions to decrease blood coagulation and prevent extension of the thrombus have been advised recently they also are used to prevent postoperative thrombosis after embolectomy Opiates are used to control pain Warm drinks alcohol and papaverine intravenously

intravenously and heparin may be combined with surgery to improve results Surgical measures include embolectomy concomitant vein ligation and amputation Embolectomy is indicated (1) when the condition is certainly not over 24 and preferably not over 10 hours old (2) when there are no medical contraindications to surgery or multiple emboli and (3) when there has been lack of improvement or progression under conservative treatment If marked arteriosclerosis is present and the condition is more than 10–12 hours old or if there is associated peripheral vascular disease or inflammation surgery probably will be useless because of the danger of thrombosis recurring

Varicose Veins in Soldiers C W Clark (R C A M C) states that varicosities are common among soldiers either because they are not noted at enlistment or because slight varicosities present enlarge under service conditions Men who had injection therapy prior to enlistment with apparently good results develop recurrences under arduous training

The following tests are useful in examination (1) cough test (2) Trendelenburg constriction test (3) three tourniquet test of Ochsner and Mahorner and (4) patency *of deep circulation Perthes test as usually employed* does not necessarily indicate deep venous obstruction If results with this test are accepted as conclusive treatment may be denied patients with small saphenous or communicating venous incompetence In doubtful cases an elastic bandage may be applied from toes to knee or above the patient then walks about for some time If he complains of increased discomfort it indicates inadequate return in the deep veins

In treatment varicose veins may be classified according to the table In any but type I particularly in soldiers there may be rapid recurrence In type II following surgery and retrograde injection of sodium morrhuate the patient is kept in bed 24 hours and told to move his leg

(7) Canad M A J 50 247 250 M h 1944

operative effort it was possible to remove the basis for psychic trauma This theory helps explain failure or limitations of this as well as other forms of therapy

Peripheral Arterial Embolism is discussed by Robert D Duncan and Mark E Myers[6] (U S Marine Hosp Baltimore) *with report of a case of successfully treated brachial embolism* Peripheral embolism carries with it a high *mortality rate and a low cure rate The fault is not always* with the surgeon or medical man as many patients are seen too late for curative treatment A lapse of 10–12 hours from onset of the disease to initiation of treatment is enough to defeat all efforts at cure in a large percentage of cases One cure has been reported after 17 hours However in many cases treatment has been delayed beyond the period of possibility of recovery by a course of conservative management or by lack of recognition or of realization *of necessity for emergency treatment Brachial* embolism yields a better prognosis than emboli in other situations but failure still results in at least 60 per cent of cases

Diagnosis of peripheral embolism is comparatively simple The usual symptom is localized sudden agonizing pain in a limb with tenderness over the point of lodgment of the embolus Pulsations are absent and the limb is cold white and paralyzed The most common sites are *femoral artery (44 per cent) iliac artery (19 per cent)* brachial (17 per cent) bifurcation of the aorta (10 per cent) and popliteal artery (10 per cent) The main point in differential diagnosis is to distinguish the condition from thrombosis which may occur from arteriosclerotic changes inflammation Buerger s disease and trauma

Treatment should be surgical and this should be *prompt since if conservative measures are tried* first this may result in delay that makes surgical cure impossible However certain measures such as sympathetic injection aids to collateral circulation e g pavaex boot intermittent venous occlusion indirect heat papaverine

(6) Am J S g 62 34 38 Oct be 1943

condyle is done Extensive operations to dissect out the communicating vein are unnecessary In type V provided the ulcer is relatively clean with no great activity of infection high ligation division and retrograde injection of the great saphenous vein combined with use of an elastoplast bandage and ambulant treatment produces excellent results

Results of this method of treatment were eminently satisfactory in 375 ligations and retrograde injections performed on 231 patients High groin ligation was done for incompetence of the great saphenous vein on 300 extremities Only three patients in the entire series returned with a few small localized varicosities which were cleared up by one or two local injections Seventy five were reexamined 6–18 months after treatment and no recurrence was found

Venography of Lower Extremities E C Baker and S H Sedwitz (Youngstown O) describe a serial method for study of the venous structures of the leg

Method—The Dolan mouth test is given prior to injection to each patient Then 20 cc diodrast is injected slowly for about two minutes through a very small needle into a small vein on the dorsum of the foot or below the internal or external malleolus It is rarely necessary to cut down on a vein for injection Two lead screens are used one on either side of the top of the Bucky table they are wide enough so that the intervening space allows coverage of half a 14 × 17 in film and long enough to reach from ankle to lower abdomen Between them the extremity can be satisfactorily positioned so that the entire venous circulation of leg thigh and lower pelvis can be portrayed on serial films During the two minutes of injection six exposures are made The first two are made from the region of the ankle up after 4–5 cc dye has been injected As soon as the tube stand and Bucky tray can be shifted up two more exposures are made of the upper leg knee and lower thigh Again the tube and Bucky stand are shifted up and the last two exposures are made including upper thigh and lower pelvis These exposures are in pairs and each is made from a stereoscopic view The dye remains long enough in one place to allow differentiation between deep and superficial circulation Rapid work permits

(8) R d l gy 41 451 458 N mb 1943

frequently Usually within a few hours a discolored streak appears along the course of the vein and the thrombus can be felt The patient is walking about after 24 hours sutures are removed on the seventh day the soldier returns to his unit on the eighth to tenth day and is on light duty for one week In about 15 per cent one or two local

TREATMENT ON BASIS OF VARICOSITY TYPE

Type	Constriction Tests	Treatment
I Mild localized varicosities	Neg constriction	Injection only
II Any degree of great saphenous incompetence	Pos Trendelenburg	High ligation division retrograde injection
III Small saphenous type	Pos three tourniquet	Ligation division retrograde injection of small saphenous
IV Incompetent communicating type (thigh)	Three tourniquet proof	Low thigh or condylar ligation division retrograde injection
V Varicose vein with ulcer	Pos Trendelenburg	High ligation division retrograde injection

injections are necessary to complete the thrombosis In bilateral cases an interval of two to three days should elapse before the second leg is treated In large varicosities a groin and condylar ligation division and retrograde injection may be done at one sitting with a retrograde injection of 4 cc in each The condylar ligation is done first the vein being picked up above the medial condyle of the femur

In type III the small saphenous vein is exposed similarly in the popliteal space and ligation division and retrograde injection of 4–6 cc of 5 per cent sodium morrhuate performed The vein is just under the deep fascia which has to be divided for exposure When incompetence of the small and great saphenous veins occurs in the same leg ligation and injection of both may be done simultaneously or the small saphenous vein may be treated two or three days before the large vein

In the rare type IV ligation division and retrograde injection of the great saphenous vein well above the medial

of the extremity The stereoscopic films permit reconstruction of anatomic positions with considerable certainty

The uppermost part of the venous tree which is demonstrable is the external iliac vein often seen for several inches before the dye becomes too much diluted Near the *femoral fossa immediately* below Poupart s ligament there is normally a large valve where the internal or greater saphenous empties into the femoral vein Below this junction are often several valves about 2 in apart The femoral vein proceeds down in the region of the femoral artery winding around the inside of the thigh slightly away from the femur and continuing down the inner portion of the thigh toward the popliteal fossa it frequently divides into two or three parts which usually recombine before the popliteal fossa is reached At the upper portion of the popliteal fossa the femoral vein here normally seen as one large vein becomes the popliteal vein The latter is variable but usually breaks up into two or three main trunks which follow the divisions of the popliteal artery The two main divisions are usually the anterior and posterior tibial veins a third division the peroneal vein often appears to have its origin below the division of the popliteal into the two tibial veins coming off the posterior tibial which in turn may divide into two parts These three deep veins proceed down fairly close to the interosseous space between tibia and fibula almost to the ankle before being lost as individual trunks

The internal or greater saphenous vein starts at the femoral fossa proceeds down in superficial tissues along the inner portion of the thigh to the knee and is demonstrable as a main trunk almost to the ankle Coming off from the internal saphenous in the middle and lower thirds of the thigh are several deep communicating veins which pass in to the femoral veins Below the knee the internal saphenous frequently breaks up into many trunks which anastomose freely with the superficial circulation The external saphenous vein is usually a main trunk from the ankle up to the knee It breaks into a plexus of veins at

completion ot the six exposures during dye injection Occa sionally a fourth film is made with two exposures one on either half of the film after conclusion of the injection. Usually this is made of the upper leg and knee area

Thus a series of overlapping films is obtained from the ankle up to and including the lower pelvis The time



Fig 91—Deep block of leg nd l we th gh. The dye is pa ng up thr gh the supe fi ial c rculat on t th midpo t on of the th gh. At thi point, most f the dye goes nwa d th ough commun cat ng ein and upw d through th femoral vein. The deep c l t n s blocked n the leg and l w r h lf of the th gh

interval between the films is such that in the normal case the venous structures of leg and thigh into which the dye enters are revisualized The fourth film gives added in formation about passage of the dye in the upper portion

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the knee or above or below it this plexus passes posteriorly through the superficial tissues and empties into the internal saphenous either close to the knee or above it

The time element in spread of the dye is of some importance In younger persons with straight veins the dye passes up more quickly than in older subjects with tortuous or dilated veins Normally the dye does not remain in the thigh veins in sufficient concentration to allow visualization for longer than a minute Passage of the dye is retarded in presence of severe varicosities dilated or tortuous veins and blockage in the vein above the point of injection When a small portion of the deep circulation is blocked by thrombosis or spasm the dye passes up through the deep circulation to the point of obstruction then returns to the superficial circulation through connecting veins Having continued to the region above the block it again passes inward through the communicating veins to the deep circulation Thus the dye passes around a block in either the deep or the superficial circulation with surprising ease (Fig 91)

In diagnosis the first and most important observation in presence of old or recent thrombophlebitis is complete absence of dye in all or part of the deep circulation In recent thrombophlebitis of superficial vessels a definite block and absence of dye in part of the superficial circulation are demonstrable With occlusion of the entire deep circulation including the deep veins of the leg popliteal and femoral the dye will go up through the superficial veins reach the internal saphenous and continue through this channel into the region of the femoral fossa Usually here it passes in and up through the iliac veins

The authors feel that their method should be used before any efforts to produce sclerosis or surgery on the veins of the leg

Modern Treatment of Varicose Veins is presented by William James Moore (Glasgow) Recognition of the varicose state usually is simple but in some cases enlarged

(9) M Press 211 276 278 May 3 95-298 M 10 1944

veins may be obscured by fat In varices of the long saphenous vein the tortuous swelling ascends the antero internal aspect of the thigh and terminates at the saphenous opening in a globular swelling In varices of the short saphenous vein the wormlike vertical track is at the back of the leg Involvement of small veins results in marks like a spider s web around the malleoli Pain and dis comfort bear no direct relation to extent of varicosity Usually if the upper part of the vein is involved there is comparatively little discomfort When the lower part is affected weight of the column of blood produces pain

Principles of treatment are to (1) arrest the hemo dynamic reflux of the venous column into the superficial veins when valves are incompetent and there is pro gressive increase in intravenous tension (2) force the superficial venous column from the unsupported subcutane ous vein into the deep muscular trunks when they are not obstructed by previous disease (3) effect obliteration of diseased venous tracts and (4) prevent entrance of blood into superficial veins from the deep intramuscular trunks by obliterating the anastomotic branches Before treatment is instituted to obliterate the superficial veins competence of the communicating deep veins must be determined by the Trendelenburg Ochsner and Mahorner and Mayo tests

Method of treatment depends on type of varicosity re sult of preliminary clinical tests the patient s condition and co operation and surgical preference Usually only when the patient refuses or presents contraindications to other treatment are palliative measures used These in clude rest in bed with legs elevated bandaging avoidance of prolonged exercise and standing and attention to general health Injection treatment is indicated when operation is refused or when despite operation small varices persist Otherwise indications are pain (the so called varicose neuralgia) discomfort and swelling of feet and legs after walking degenerative changes in skin and subcutaneous tissues ulceration patency of deep veins or

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on solid edema caused by chronic venous disturbance tight bandages are applied The malleolar ulcer usually caused by femoral thrombosis is irritable and painful pads and bandages are applied and pain is controlled with sedatives If elastoplast does not relieve eczematous ulcer creolin and ichthopaste are tried Treatment of a large ulcer (up to 140 sq in) depends on condition of arterial blood supply Rest in bed is necessary to reduce swelling injection skin grafting and bandaging are suggested remedies

Mild types of eczema yield to tight bandaging When dermatitis occurs around the ulcer it is dressed with cereban and bandaged *In some allergic patients adhesive* plasters produce intense inflammation dressings should be changed to cereban or ichthopaste but compression should be maintained

Success of treatment of varicose ulcers depends on diagnostic accuracy wise selection of treatment and the patient s co operation If any doubt or suspicion of malignancy exists the ulcer should be excised electrosurgically

Varicose Veins R A Larson and F L Smith present an evaluation of observations on 491 patients (335 women and 156 men) A definite familial history of varicosities was given by 213 Varicosities appeared during pregnancy or after parturition in 161 of the 335 women History of previous superficial or deep thrombophlebitis was elicited in 53 cases Some types of prolonged illnesses were noted in 52 Trauma was mentioned by 37 patients as playing a role in production of their varicosities

Aching pains and edema were the most prevalent symptoms of varicose veins in the series Apparently most patients defer surgical aid until the condition is far advanced in 60 per cent stasis sequelae had developed before the patients presented themselves at the Clinic

Combined high ligation division and injection at the saphenofemoral junction was deemed the procedure of choice in 395 cases In 96 varicosities existed without in

(1) P oc St ff M t M y Cl 18 400 403 O t 20 1943

deficiency of arterial circulation Contraindications are cardiovascular conditions kidney disease thrombophlebitis occlusion of deep veins pregnancy deficiency of arterial supply to the extremity pressure of pelvic tumors or cysts and diabetes The mixed twin injection advocated by Simpson Harvey is specially recommended for large veins There is no danger of cinchonism as quinine is precipitated as a gelatinous deposit of quinine salicylate which adheres firmly to the venous wall The froth method is recommended for treatment of spider veins Ligation and injection should always be used when the saphenou valves are incompetent Site of ligation is at the entrance of the saphenous vein into the femoral Ligation at mid thigh lower thigh and of the external saphenous at its entrance into the popliteal vein are all secondary Sub cutaneous ligation has been recommended by several authorities when the upper part of the long saphenous vein is varicose because pressure of the blood column *defeats attempts at thrombosis*

Excision is not now commonly practiced but is recom mended for patients with recurrent phlebitis or a large venous pouch If a recent thrombosis is present the af fected segment should be removed to prevent embolism Exposure double ligation and excision with or without injection is seldom necessary but is advocated when there is definite venous thrill on coughing Best results are ob tained when ½–1 in of vein is excised

Complications that may be associated with varico ti are ulceration phlebitis hemorrhage thrombosis neuralgia and varicose dermatitis or eczema The most troublesome is ulceration The indolent abrasion is treated by strap ping with elastoplast A small ulcer at the inferior ex tremity of a varicose vein is treated by obliteration of veins by injection from above downward The medium ulcer (to 14 sq in in area) is treated by pulling the *edges together and strapping tightly* with elastoplast from toe to knee with multiple injections to thigh and leg veins after healing of the ulcer For an indurated ulcer situated

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VENOUS LIGATION IN 395 CASES

Lower Extremity Involved	Great Saphenous Vein	Small Saphenous Vein
Both	168 (43%)	12 (3%)
Right	74 (19%)	12 (3%)
Left	125 (31%)	4 (1%)
Total	367 (93%)	28 (7%)

trunk In the remaining 28 cases incompetency of the small saphenous vein was not associated with incompetency of the great saphenous vein This fact can be determined by using the modification of the Trendelenburg test as described by Heyerdale and Anderson Although this group in which the small saphenous vein was incompetent is small numerically it should not be ignored for if independent incompetency of the small saphenous vein is properly considered the more extensive operations for ligation of communicating branches will not be necessary The number of ligations in this series and the limbs affected are given in the table

Dicumarol Therapy in Thrombotic Emergencies. James A Evans (Lahey Clinic) reports results of treatment of 56 patients with dicumarol alone or combined with heparin Two deaths occurred (4 per cent) one of which can be attributed unequivocally to dicumarol poisoning and hemorrhage Hemorrhagic phenomena were evident in eight cases (14 per cent) These complications emphasize the dangers and disadvantages of dicumarol but obvious advantages apparently outweigh these if adequate laboratory facilities are available and proper precautions are observed The principal precaution is determination of morning prothrombin time before ordering the daily maintenance dose of dicumarol Combined use of heparin and dicumarol is considered safe only if doses of heparin are controlled by twice daily determinations

(2) New England J Med 230 131 135 Feb 3 1944

of coagulation time of the blood and doses of dicumarol by determinations of prothrombin time made once daily

One benign and no fatal pulmonary embolism occurred in 46 cases of venous thrombosis This series is not large enough to draw the conclusion that venous ligation is unnecessary If a patient over 50 has a warning benign pulmonary embolism venous ligation is still indicated If more data are accumulated on the effect of dicumarol from other workers venous ligation may prove unnecessary except in rare cases of recurrent emboli after anticoagulation treatment

Operative Attack on Organic Peripheral Vascular Disease is discussed by Ridgeway Trimble William S Cheney and William R Moses (Baltimore City Hosp) It is well known that certain functional disorders of the nervous mechanism of the blood vessels cause either a vasoconstriction or a vasodilatation and that the disorders causing vasoconstriction can be dramatically relieved by sympathectomy It is not generally appreciated however that many organic vascular diseases have an associated vasomotor spasm which may be the cumulative factor responsible for the ensuing gangrene Death of the part affected is due many times not to the original arterial disease but to the superimposed constriction of accompanying smaller vessels Recognition of this fact and subsequent operative removal of the nervous mechanism causing the vasoconstriction will in proper cases cure pain and actually save the part from death from gangrene

The functional vasoconstricting lesions of local distribution in Brown and Henderson s clinicopathologic classification (see Table) are known to be improved following sympathectomy Even certain types of functional vasoconstricting lesions of general distribution are relieved by sympathectomy The great organic group however is not generally supposed to be susceptible to the sympathetic approach but the authors believe that many

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thetic ganglions or by intrathecal injection (spinal anesthesia) A favorable local result is shown by a rise in temperature a more healthy ro y color to the skin absence of sweating and subsidence of pain Fine determination of these re ults can be made by various calorimetric oscillometric and plethysmographic records

If by such tests a diseased extremity shows definite circulatory improvement a sympathectomy must be considered seriously However a negative response to preliminary tests should not preclude the possibility of aid hrough sympathectomy In many patients during a preliminary test by novocain sympathetic injection the temperature of the foot is not increased nor is the color of the ffected toes improved although the pain usually ceases Nevertheless following sympathectomy there are rise in mperature improvement in color and cessation of pain

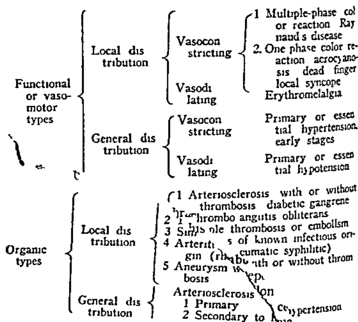
Thrombosis and Embolism Review on 202 Patients **reated by Femoral Vein Interruption** is presented by rthur W Allen Robert R Linton and Gordon A Don dson At Massachusetts General Hospital in 1937 this peration was performed once in 1941 55 times and in 1942 211 times This great increase was due to increased onfidence in the procedure and to a greater number of lateral operations They believe that femoral vein interuption for prevention of pulmonary embolism is simple d safe and can be carried out on extremely ill patients o deaths resulted from this procedure in the 202 patients Indications are usually apparent Pulmonary infarcts nderness over the leg veins swelling of the leg however ght dilated superficial v ins di comfort in the calf uscles if the foot i ely dorsiflexed (Homans gn) and slight elevat mperature pulse rate and spirations are all tudes Usually the de ision as to de on one or two of ese criteria re present In most ases bilateral undertaken Un

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patients in this group can be benefited by sympathectomy

Correct differentiation of the vascular disturbances of the extremities must be made in each patient Most significant is the search for pulsation in all palpable

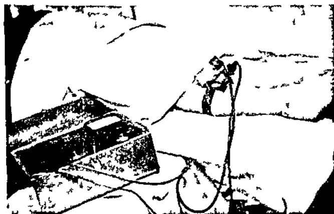
CLINICAL CLASSIFICATION OF ARTERIAL VASCULAR DISEASE



arteries The role played by vasomotor contraction must next be determined by one or several of various test Warming the rest of the body generally or warming extremities other than those to be tested will through reflex inhibition of the tone of the vasoconstrictor center cause dilatation of the vessels in the involved extremity and consequent rise in temperature and computable blood flow if vasomotor spasm has been an appreciable factor in the disease of the extremity These same effects may be produced by interrupting vasomotor control of the extremity either by novocain injection into the sympa

permanent swelling or usual sequelae of postphlebitic eczema and ulcer so frequent following conservative treatment of thrombophlebitis The earlier diagnosis is made and vein interruption is done the shorter the period of convalescence

Dermofluorometer, an instrument for objective measurement of fluorescence of the skin and organs and objective determination of circulation time and capillary permeability is described by Kurt Lange and S E Krewer (New York Med College) This simple method



F g 9 —D mofl m t 1b h t t g f l ght d ph t t l ta h l t f t t l b

can be used routinely to locate exactly the site of a vascular occlusion or to ascertain how much blood flow to an organ or section of skin is diminished by difference in depth of staining per unit of time Since fluorescence of fluorescein is excited by blue and violet visible light as well as ultraviolet light incandescent blue light is convenient for actual measurements since it is smaller and produces less heat

INSTRUMENT —A compact unit combines the incandescent

(6) J Lab & Clin Med 8 1746 1750 Nov 1943

lateral interruption may be safely done as indications arise in younger patients In patients over 40 bilateral interruption at one sitting should be the rule

The authors are convinced of the safety of mechanical removal of the thrombus from the vein by aspiration It reduces pain and swelling in the leg and hastens recovery Sequelae are not severe or disabling Postoperative edema is the most serious of these but patients complain so little about it that it is relatively unimportant Eleven of the 202 patients had infarcts 2 of them died after leaving the hospital The other nine recovered four had cardiac conditions One patient who had infarcts after prostatectomy continued to have emboli following bilateral superficial femoral interruption He was given heparin for eight days and recovered Eight of the 11 patients with infarcts had bilateral interruption Twelve patients died of their disease after femoral vein interruption all deaths were thought due to causes unrelated to this procedure One patient who had infarcts and died after leaving the hospital may have had a fatal embolus from the uninterrupted vein on the opposite side

Thrombophlebitis and Pulmonary Embolism A W Allen (Massachusetts Gen l Hosp) states that pulmonary infarcts come from the deep veins of the legs in 95 per cent of cases *Thrombosis of the leg veins can often* be diagnosed prior to pulmonary infarct Interruption of superficial femoral veins has been carried out on 202 patients without serious sequelae In fact results are so satisfactory and have received such approbation by physicians in the medical department that they usually refer the patient direct for surgical ligation without waiting for such recommendation from a consulting surgeon

The operation is simple and can be done on extremely ill patients without risk *It prevents fatal pulmonary* embolus and reduces the convalescence period of thrombophlebitis The postoperative edema of the legs is transient and not disabling There has been no evidence of

(5) K (ky M J 43 160 163 J 1944

cent solution) is injected intravenously and the time elapsing between beginning the injection and initial deflection is measured with a stop watch This constitutes circulation time to this area A mouthpiece made from transparent lucite can be used to determine circulation to the lip or gums if this is preferred to visual observation Subsequently all test spots are touched with the instrument and the deflections of the photometer are read Background readings are subtracted to obtain absolute fluorescein value Thus a curve is obtained for each area of the body surface which indicates how much blood and with it fluorescein are reaching this district per time unit

To standardize values found with different instruments the following basis was adopted one skin unit is the deflection caused by an alkaline fluorescein solution of 1 50 000 000 in a cuvette of 5 mm depth the glass of which shows no absorption for the exciting light

The first part of the curve thus obtained depends primarily on amount of blood reaching a given area per unit of time and on capillary permeability Changes in plasma proteins within physiologic limits do not influence the amount of fluorescein available for diffusion into tissue fluids The last part of the curve is strongly influenced by excretory function of the kidney

In myxedema capillary permeability is especially high and this may be the explanation for the peculiar skin condition and the tendency to form transudates especially in the pericardium By applying the instrument to different parts of the extremity of a patient with peripheral vascular disease often the exact place at which the artery narrows decidedly can be foretold At the corresponding skin level skin fluorescence suddenly decreases At the same time circulation time to a limb with generalized arteriosclerosis is usually markedly prolonged

[Sp iali t m th f 11 tell me that this instrument is a most valuable contribution to the diagnosis and treatment of peripheral vascular diseases —F1]

Effect of Digitalis on Clotting Mechanism Geza de Takats P A Trump and N C Gilbert (Northwestern Univ) state that clinical studies and animal experi

(7) J A M A 1 5 840 845 J 1 1944

light source and the phototube in rigid relative po ition (Fig 92) The exciting (primary) blue light impinges on the body while the yellow green fluore cent (secondary) light (i e light of longer wavelength than the primary light) of the blood stream evoked by the blue light is registered by the phototube primary light must be prevented from reaching the phototube by reflection This i accomplished by a filter F_1 (Fig 93) in the primary light beam and filter F set in front of the phototube Filter F_1 transmits blue light only and ab orbs practically all light of a wavelength longer than 5 000

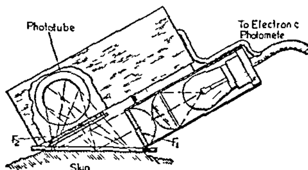


Fig 93 — D g f l t I bl filt f t of light F y ll w fil f t f F_1 t be

A Conver ely filter F absorb all light of a wavelength shorter than 5 000 A and transmit mainly yellow green light characteristic of the fluore cence of fluore cein Since all the filters have a small undesirable leakage in the infra red range the phototube selected is entirely in en itive to infra red radia tion *Because of these provi ion light registered by the* phototube before injection of fluore cein is negligible and i taken care of by a background reading which give the actual degree of deflection of the in trument before injection The deflection following injection therefore represents th effect of this injection quantitatively Current output of the phototube is amplified approximately 3 × 10 in the electronic photometer

TECHNIC —In a darkened room everal te t pots of the body to be examined are touched with the instrument and background deflection noted The in trument is then at tached with a usual rubber trap to the pot hich circu lation time i to be observed Fluore cein 5 per

DISEASES *of the* DIGESTIVE SYSTEM *and* METABOLISM

GEORGE B EUSTERMAN M D

ments indicate that digitalis favors the tendency to thrombosis This is especially significant in patients in whom other factors such as stasis or infection are present This effect of digitalis can be determined by a simple test of the clotting mechanism consisting of serial determinations of capillary coagulation time after injection of 10 mg heparin Such study of heparin tolerance is far more sensitive than single determinations of coagulation time and more readily available for clinical use than determination of prothrombin levels

Auricular and ventricular thrombi and subsequent emboli have been observed in digitalized patients Besides the usual anticoagulants heparin and dicumarol sodium tetrathionate seems to be capable of counteracting the thrombogenic property of digitalis

PART V

DISEASES OF THE DIGESTIVE SYSTEM AND METABOLISM

DISEASES OF THE ESOPHAGUS, STOMACH AND DUODENUM

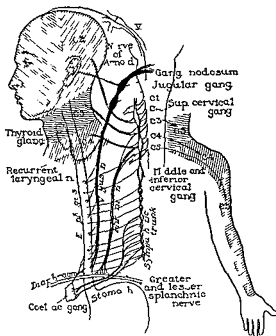
General Observations on Cardiospasm Asher Winkelstein (Mount Sinai Hosp, New York City) states that cardiospasm is in most cases a psychosomatic disease As an example of numerous cases that illustrate this he cites one of a girl 19 who had been raped five years before by a man 50 He threatened to kill her if she informed her family The next day dysphagia and regurgitation began and persisted Radiography revealed a widely dilated esophagus and food retention for several hours After the first sexual incident she had affairs with various men voluntarily and lived in constant dread of discovery by her parents who considered her a model child

Organic disease of the vagus nerve and reflex causes also have etiologic significance The condition is not a spasm but an achalasia or failure to open actively Dilatation persists despite clinical improvement Elongation esophagitis and diverticula may develop Esophagoscopy is imperative to exclude neoplasm and peptic esophagitis *Psychotherapy and insertion of the soft mercury weighted* rubber esophageal bougie are the two best forms of treatment for patients with a straight dilated esophagus For those with an elongated figure of S esophagus esophagogastrostomy is indicated Artificial hyperpyrexia deserves further study as a therapeutic agent

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medulla vagus fibers and the sensory nucleus are in close apposition to the descending tract of the trigeminal nerve which constitutes a possible route for pain referred to the face in esophageal disorders The somatic sensory nerve from the nodose ganglion of the vagus (the nerve



F 94—Hyp l t cal f t mis (ply f soph g f esophageal p d pos bl p th ys

of Arnold) innervates the external auditory canal and constitutes the most logical pathway for the reference of pain to the ear which is occasionally seen in disease of the esophagus (Fig 94)

Marked differences in opinion exist among neuro-anatomists as to the origin of the sympathetic nerve supply of the esophagus From various observations however it

[Contrary to the opinion of the author, my colleagues in endoscopy favor almost exclusively the Plummer-Vinson hydrostatic dilator when treatment by this procedure is indicated. In experienced hands the danger is minimal. When complications occur, which is rarely, the immediate co-operation of the thoracic surgeon invariably prevents a fatal outcome. Results of treatment by other types of instruments in my experience, are often incomplete or repeated dilatation is necessary. Not infrequently a complete cure is obtained promptly by one treatment with the hydrostatic dilator after prolonged and unsuccessful attempts by other forms of instrumentation.—Ed.]

Esophageal Pain is discussed by Herman J. Moersch and James Rex Miller (Mayo Clinic).[1] Pain is often one of the earliest manifestations of esophageal disease but if not associated with dysphagia it is frequently misinterpreted as functional in origin. An obstacle to clear understanding of the importance of esophageal pain in esophageal disturbances is the paucity of knowledge concerning innervation of the esophagus. It is generally agreed that the innervation is derived from the vagus and the sympathetic system and that the vagus nerve furnishes a rich supply to the esophagus. The exact anatomy of the distribution of the branches from these main systems to the esophagus, however, is not well described.

According to Kuntz, the upper portion of the esophagus is supplied by the recurrent laryngeal nerves and the lower portion by the esophageal plexus, which is formed by intermingling of the right and left vagus nerves. While all authorities agree that the vagus nerve is a mixed nerve, many do not believe that it is a factor in conducting afferent pain impulses from the esophagus. Others, however, believe that the nerve must be a factor in conduction of esophageal pain. Patten stated that it is the consensus that pain in cardiospasm is conveyed by vagal afferent fibers. Miller stated that although the vagus nerve as a pathway for conduction of pain has been considered inconsequential, its distribution would best explain some of the atypical radiation of pain that occurs in angina pectoris. The nerve has communications with the glossopharyngeal nerve, the spinal accessory nerve and the first and second cervical nerves. Centrally, in the

(1) Gastroenterology 1:821-831, Sept.-Dec. 1943.

was roentgen evidence of disturbed function of the esophagus in all with a varying degree of stenosis in three. Four were examined on one or more occasions by the esophagoscope and biopsy was performed in two

It appears that a disturbance of esophageal function is characteristic of generalized scleroderma and that it is likely to appear early in the course of the disease The esophageal disturbances are characterized by loss of peri stalsis and relaxation and mild dilatation of the lower two thirds down to the phrenic ampulla and probably some atony of the cardiac sphincter occurring as a direct result of the sclerodermic proce s There are inability to swallow more than a few mouthfuls of fluid rapidly difficulty in swallowing while lying down and sensation of fulness behind the sternum or of a weight on the chest for a few moments after swallowing owing to delayed emptying of the esophagus Burning pain is noted behind the sternum about an hour after meal worse on lying down and particularly on lying to the left side caused probably by regurgitation of gastric contents into the *esophagus and resulting chronic esophagitis* Chronic ulceration in the lower third of the esophagus localized chiefly to the region just above the phrenic ampulla is probably a direct result of the esophagitis with scleroder mic changes as a predi posing factor Stricture formation in the later stages is limited to the region immediately above the phrenic ampulla of the esophagus

Biopsy study revealed changes in the connective tis ue of the submucosa which suggest sclerodermic change

[Another of the numerous factors giving rise to esophageal dysfunction i avitaminosis The mechanism underlying such disorder of function whether neural or as the result of local t ssue change is a matter of controversy The intact state f Auerbach s plexus and nerve ganglions in scleroderma lends support to the contenti n that local ti ue changes are primarily responsible — Ed]

Roentgen Appearance of Gastro Intestinal Tract in Scleroderma. Clayton H Hale and Richard Schatzki (Massachusetts Gen l Hosp) describe findings in 22 cases Esophageal changes found in 13 cases varied some

might be assumed that the esophagus likely derives its sympathetic fibers from the inferior cervical ganglion and the first to the ninth thoracic sympathetic ganglion Most authors assume that the sympathetic nerves conduct the pain sensation The central pathway for visceral afferent sympathetic fibers is thought to follow the same course as do the nerves transmitting somatic pain

While the phrenic nerve does not supply the esophagus it may convey pain in esophageal disease Owing to the close relationship between the lower portion of the esophagus and the diaphragm disturbances in the esophagus may produce irritation of the diaphragm Such pain stimuli may be transmitted by way of the phrenic nerve which arises from the fourth cervical segment with less constant branches from the third and fifth segments and rarely from the second segment (Fig 94)

Clinical observations bear out experimental evidence that esophageal pain is primarily dependent on the state of tension of the esophagus and its structural adaptability These in turn are markedly influenced by many extraneous factors The character of esophageal pain varies considerably The more severe the pain becomes the wider its distribution Pain due to disturbances in the upper portion of the esophagus is more likely to be situated over the thorax at a point corresponding to the underlying esophageal lesion Disturbances in the lower portion of the esophagus as might be anticipated from the source of the nerve supply as well as from the close relationship with the diaphragm give rise to a much more diversified distribution of pain

Lesions of the Esophagus in Generalized Progressive Scleroderma. John R Lindsay Frederic E Templeton and Stephen Rothman[1] (Univ of Chicago) studied five consecutive cases which were clinically and histologically typical of diffuse scleroderma The patients three men and two women presented clinical evidence of a disturbance of the swallowing mechanism varying apparently only in the stage of the esophageal lesion There

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Gastrointestinal changes in scleroderma are important clinically. Symptoms may simulate those of cardiospasm, deficiency disease or ileus. The changes could be explained on the basis of local changes in the intestines or



Fig 97 (left).—Dilated loop of j j m d g l j ot my
Fig 98 (right).—S tee d y ft p t E tally m l g t t t l t t Th had b c f l l ymptom

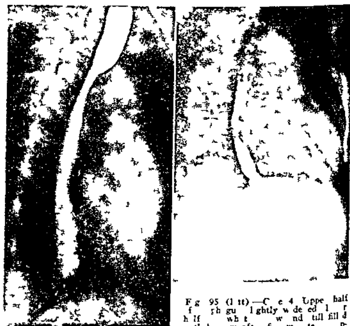
in the governing nervous mechanism. Rapid recurrence of changes in the jejunum in the aforementioned case strongly suggests a pathologic condition of the nervous mechanism.

Experimental Production of Acute and Subacute Gastric Ulcers in Cats by Intramuscular Injection of Caffeine in Beeswax. J. A. Roth and A. C. Ivy[5] (Northwestern Univ.) produced gastric ulcers (Fig 99) by prolonged continuous intramuscular administration of caffeine in a mixture of beeswax and mineral oil. Factors that may play a role in production of these ulcers are hypersecretion, vasodilatation, engorgement, hypermotility and cellular toxicity (Fig 100).

There is no agreement as to effect of caffeine and its

(5) G ter l gy 2 4 8 Ap l 1944

what but consisted mainly in delayed emptying combined with decrease in peristalsis of the esophagus (Figs 95 and 96) The small intestine showed significant changes in four patients with localized widening usually of the



F g 95 (l tt) —C e 4 Uppe half f rh gu l ghtly w de ed l r h lf wh t w nd till fill d w th l m aft fi m te p
ght po t Loc l ed p t f tr ct n l m bo e d ph gm
F g 96 (abo ght) —Ca 9 F ftee m t s aft ba um wall h g n ly f ll f l m l ttl f y pe talt ct ty

proximal loops and marked delay in passage of barium through these loops One patient with minimal scleroderma showed markedly dilated loops of the upper jejunum confirmed at operation (Fig 97) Resection of the dilated part of the bowel did not prevent recurrent dilatation of the jejunum beyond the area of original dilatation and the patient died Autopsy failed to show any cause for the dilatation There was questionable involvement of the colon in two cases indicated by a peculiar sacculation with areas of increased rigidity between areas of sacculation in one

development of ulceration Direct observation of a mucosal stoma in the cat shows persistent hyperemia after intravenous administration of caffeine followed by cyanosis Preliminary experiments indicate that caffeine does not induce pylorospasm but rather increases peristaltic contractions to accelerate gastric emptying It has been suggested that trauma from vigorous contractions might initiate a mucosal defect when the mucosa is engorged

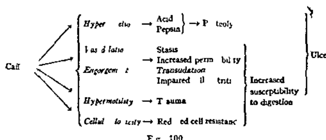


Fig 100

and edematous In experiments on man Wolf and Wolff observed that intense anxiety hostility and resentment were accompanied by severe and prolonged engorgement hypermotility and hypersecretion in the stomach Mucosal erosions and hemorrhages were readily induced by trifling trauma and frequently bleeding points appeared spontaneously as a result of vigorous contractions of the stomach wall Since acute experiments showed diffuse desquamation of the mucosal epithelium in large areas this suggests that caffeine may provide a factor of cellular toxicity in the doses used and hence lower resistance of cells to the ulcerative process

The consensus today is that ulcer of the stomach is in some way due to local loss of resistance by the mucous membrane to digestant activity of the gastric juice Although the mechanism of production of stomach ulcer by caffeine injections in cats is purely speculative experimental results imply that excessive use of caffeine containing beverages might play a contributory role in pathogenesis of gastroduodenal ulcers in man In view of these findings

beverages on gastric secretion However the authors have considerable evidence that caffeine and coffee taken orally are potent stimulants of both acid and pepsin content of gastric juice in man and cat but not in the dog in the same doses Intramuscular or intravenous administration of caffeine likewise provokes copious flow of gastric secretion Caffeine does not seem to give much stimulation to mucous secretion Dragstedt believes that exces

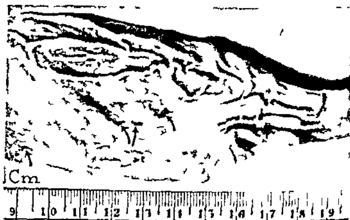


Fig 99 —La ge p pyl l n cat g d ly tram sc la m pl ntat ns of 300 mg ffe (b e) n m al l bee w x m tu D ed aft 11 d y

sive continuous secretion of gastric juice with relative or absolute deficient neutralization is a major factor in pathogenesis of human gastroduodenal ulcers It seems highly probable that ulcers produced in the authors study developed partly in consequence of presence in the empty stomach of a strongly acid gastric juice over a long period There may or may not be a neurogenic factor by virtue of excitatory action of caffeine on the central nervous system

Microscopic studies suggest that the marked vasodilatation and engorgement might in turn give rise to stasis increased capillary permeability transudation and impaired cell nutrition all of which would contribute to

use of coffee so affect the gastric mucosa and glands as to predispose to gastroduodenal ulceration in susceptible subjects

Experiments on effect of caffeine on animals have been inconclusive but Roth s observations on man showed that intramuscular injection of 4 gr caffeine base as caffeine sodium benzoate cause copious secretion of gastric juice Response is usually completed in one hour though some subjects secrete at a high level for two or three hours Oral administration of the same dose in 200 cc water stimulates to about the same extent and 1 mg atropine sulfate subcutaneously decidedly reduces but does not abolish the response A dose as small as 1 1/5 gr caffeine orally in 200 cc water definitely stimulates When 500 cc coffee (Fig 101) is given via stomach tube to avoid psychic stimulation gastric secretion is decidedly stimulated In some subjects response is completed in one hour in others it continues two or three hours Three hundred cc Sanka which contains over 1 gr caffeine also stimulates gastric secretion Alcohol (50 cc of 7 per cent) and 4 gr caffeine manifest a synergistic stimulation of gastric secretion Thus the practice of drinking coffee in relation to alcoholic beverages places the stomach and duodenum of the person susceptible to peptic ulcer under considerable strain Results on normal subjects show that histamine and caffeine act synergistically in stimulating the gastric glands This leads to the suspicion that patients with peptic ulcer will show a low threshold to caffeine stimulation

[The e contributions by Iv a d h a sociates naturally arouse peculat on as to the gene i ot chronic ga troduodenal ulcerat on Most biologists and gen tici ts tress the ndogenous factor (constitution diathesis) a rather ntangible one to me whereas most clin cian are impressed th the exogenous factor Chronic ulcer is str kingly a disease of civilization Surely the increasing emotional and phy ical stress the abuse of alcohol tobacco coffee and cokes and the partaking of hast ly eaten h ghly sea oned foods that our vaunted complex civilization increasingly entails seem ufficient reason for the prevalence of this disorder—Ed.]

Evidence That Body Irritations or Emotions Retard Gastric Evacuation, Not by Producing Pylorospasm but by Depressing Gastric Motility, is presented by J P

and marked stimulation of gastric secretion produced in man by oral or parenteral administration of caffeine it is suggested that use of caffeine beverages be restricted in treatment of the peptic ulcer patient

Some Recent Developments in Physiology of Stomach and Intestine Which Pertain to Management of Peptic Ulcer are discussed by A C Ivy[6] (Northwestern Univ) Experiments on animals with enterogastrone immunization against gastrojejunal ulcer provide a basis for the

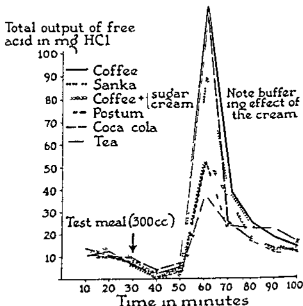


Fig 101

hope that in time it may be possible to increase resistance of gastric and duodenal mucosa to ulceration and decrease the incidence of recurrences of peptic ulcer in susceptible patients

Laboratory evidence supports the view that consumption of alcoholic beverages excessive smoking and excessive

(6) B ll N w Y k Acad M I 0 5 14 Jan

degree where they cannot react even to fat stimulation may account for failure of some uncomplicated duodenal ulcers to respond to medical management

The duodenal mechanism concerned with gastric secretion is believed to be largely responsible for diminishing gastric acidity seen in the second half of a normal fractional gastric analysis and is an expression of the self regulating mechanism of gastric secretion

Shay regards the term peptic ulcer as undesirable because gastric and duodenal ulcers are not derived from the same cause and in their effects on gastric physiologic mechanisms they are different diseases despite the fact that both are ulcerative processes

[This article is in essence a summary of a series of articles previously published by Shay and his associates To serious students of normal and abnormal gastric physiology this contribution will repay careful perusal in its entirety for it contains many illuminating features of both theoretical and practical interest —Ed]

Influence of Duodenal Contents on Intragastric Acidity Authi Kesavalu and Frank C Mann (Mayo Clinic) studied the neutralizing capacity of the duodenal contents on the acidity of the gastric contents in an attempt to ascertain the role played by duodenal regurgitation in controlling gastric acidity under physiologic conditions Two groups of dogs were studied One group had gastric (pyloric) fistulas and the other had isolated fundic pouches The duodenum was short circuited into the fundic region of the stomach in both groups so that all the duodenal contents passed into the stomach No attempt was made to determine whether the quantity and quality of the duodenal contents were normal under the conditions of the experiment

Gastric samples were collected through the pyloric fistula every 15 minute for eight hours or more while the animals were fasting and after feeding and the pH of the samples was determined electrometrically The secretion from the fundic pouch was collected 3 6 and 24 hours after feeding the quantity was noted and the free and total acidities were determined titrimetrically

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Quigley H J Brvor M R Read and P L Brofman (Western Reserve Univ) The effect on motor activity of the pyloric sphincter of emotions or of a variety of noxious bodily stimuli applied to somatic and visceral structures was determined on trained dogs by several rather direct methods Under such stimulation the pyloric sphincter region (antrum sphincter and bulb) tended to behave as a unit in action the sphincter was similar not contrary to the antrum Emotions and noxious stimuli did not produce pylorospasm but tended to inhibit the entire sphincter region and retarded gastric evacuation by decreasing antral peristalsis The delayed evacuation was not due to pylorospasm but developed despite pyloric relaxation The claim that pylorospasm is readily produced by emotion or noxious bodily stimuli receives little support from this study or from a critical consideration of the clinical evidence

Pathologic Physiology of Gastric and Duodenal Ulcer Harry Shay (Philadelphia) states that gastric and duodenal ulcers produce changes in gastric motor and secretory functions Changes caused by the former can be related to action of the lesion on local gastric mechanisms Changes in gastric function produced by duodenal ulcer are attributed to damage of duodenal mechanisms whose activities are concerned with decreasing gastric evacuation and secretion The most sensitive portion of these duodenal mechanisms is located in the cap the usual site of duodenal ulcer Usually the mechanisms are obtunded and not destroyed by the ulcer and may recover with healing of the lesion Probably the only reliable criterion of healing of a duodenal ulcer is return of gastric motor and secretory function to normal

Although obtunded by the ulcer and associated duodenitis duodenal mechanisms in most instances of active ulcer can still respond to stimulation by fat On this fact rests part of the therapeutic value of milk and cream in the ulcer diet Impairment of duodenal mechanisms to a

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(8) B ll N w Y k A d Med. 0 64 291 M y 194

tion (Fig 102) This is similar to the augmented gastric secretion that occurs when alkalis are administered orally

The results of these experiments appear to demonstrate that presence of even the entire duodenal contents in the stomach does not cause effective neutralization buffering and dilution of gastric acidity in either the fasting or the digesting state It is questionable if the slight and infrequent duodenal regurgitation that occurs normally can be a primary and essential factor in controlling intragastric acidity

Action of Alkaline Preparations in the Stomach was tudied in 10 normal subjects by Jose Opizzi Gastric analyses were made according to the Rehfuss fractional technic under physiologic conditions and after ingestion of sodium bicarbonate calcium magnesium carbonate calcium carbonate tricalcium phosphate trisilicate of magnesium aluminum hydroxide sodium citrate and disodium phosphate Each was given in fasting dose of 0 5 Gm and 2 Gm after a test meal

Sodium bicarbonate 0 5 Gm proved more harmful than beneficial as a gastric neutralizer with compensatory reaction It was effective in neutralizing acid in 2 Gm. doses for a short period after the test meal Calcium magnesium carbonate should not be used Calcium carbonate should not be used clinically because of secondary stimulation of acid secretion its neutralizing effect is slight in intensity and duration Tricalcium phosphate is condemned for similar reasons Trisilicate of magnesium showed good neutralization with little secondary effect in both fasting doses and larger amounts given after test meal Magnesium hydroxide also produced satisfactory and lasting neutralizing effect was well tolerated and secondary effect was slight Aluminum hydroxide was a good neutralizer in both doses with very little secondary action Sodium citrate was completely ineffective in both dosages Disodium phosphate was a weak neutralizer in both doses producing great increase in total acidity

These experiments prove that many alkaline prepara

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The results showed that duodenal regurgitation into the stomach as shown by presence of visible bile occurs infrequently in the fasting state as well as during digestion Its presence was not associated however with alterations of the acidity curve of the gastric contents

After the entire duodenal contents had been diverted into the stomach some dogs with pyloric fistulas showed an increase of gastric acidity while others showed some

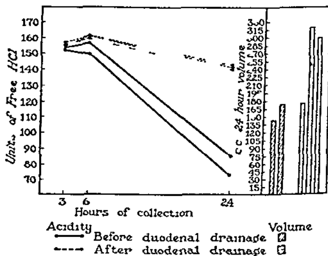
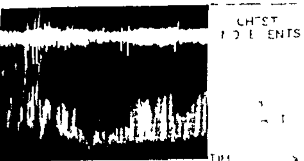


Fig 102—Fr e dity f sec t n of f d c pouch bef e nd ft r d od nal d n g to toma h Ea h curv n a e ge for two weeks.

reduction although not marked Gastric evacuation time was definitely decreased after gastrojejunostomy (modified Polya) which was a part of the operative procedure in duodenal drainage This in itself might have contributed in no less degree to the reduction of gastric acidity noted in some animals (Wangensteen and coworkers) Effective neutralization or inhibition of acid secretion never occurred

In the dogs with isolated fundic pouches short circuiting of the duodenal contents into the stomach was followed by an increase of quantity and acidity of the



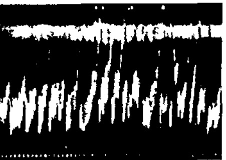


Fig 103—Kymograph ... Left ... of ... following ... Right ... 1½ h after ... D pt ... with ... temperat ... (C) ... (Wolf p 630)

tions favor gastric mucous secretion without altering acid secretion others stimulate acid secretion with resulting increased total acidity Sodium bicarbonate probably also increases mucous secretion but also dissolves it so its presence is not noted in serial determinations of gastric acidity

[As usual aluminum and magnesium hydroxide as well as magnesium trisilicate receive favorable comment However some authorities especially those of the Sippy school will disagree with the author because of his unfavorable appraisal of calcium carbonate as an antacid and with considerable justification—Ed]

Relation of Gastric Function to Nausea in Man Stewart Wolf (M C A U S) investigated changes in gastric function during nausea and correlated them with other more widespread changes in bodily function Several nauseating stimuli were applied The changes associated with the nausea resulting from each were clearcut and uniform

Following stimuli of intensity insufficient to cause nausea there occurred interruption of gastric contractions and decreased muscular tone of the stomach wall Stronger stimuli which caused actual nausea induced further changes in the stomach characterized by pallor decrease in output of hydrochloric acid and acceleration of production of mucus More widespread bodily changes were also noted including salivation sweating and tachycardia followed by bradycardia

Nausea occurred only during phases of inhibition of gastric motor activity When by combination of prostigmine hydrobromide 0 015 Gm and atropine sulfate 0 0012 Gm gastric contractions were made to continue despite strong vestibular stimulation nausea failed to occur (Fig 103) The fact that gastric motor inhibition could be blocked by drugs thereby preventing nausea suggests their possible prophylactic use against seasickness

Effect of Aluminum Hydroxide Gel on Gastric Secretion was studied in two Cope pouch dogs by W Lloyd Adams and Byron B Clark with Dorothy B Blair and

(1) J Cl I t g t 8 7 88 N mbe 1943

Effect of Certain Antacids in Man Measured by Simplified Method for Continuous Recording of Gastric pH N E Rossett and James Flexner (Bellevue Hosp) report elimination of mechanical difficulties in a method previously described Gastric juices are led from the stomach with a no 16 F duodenal tube to a standard commercial continuous flow electrode which is coupled with a Beckman pH meter and with the recording potentiometer and pumping system

Patients with gastro intestinal symptoms were studied repeatedly with this method Typical findings of examinations on five successive mornings in a patient with duodenal ulcer are shown in Figure 104 Tracings show the

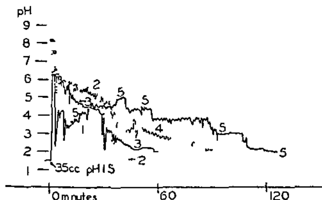


Fig 104

effect of sodium bicarbonate 1 Gm (*1*) calcium carbonate 1 Gm (*2*) 200 cc sweet milk (*3*) 200 cc milk plus 1 Gm calcium carbonate (*4*) and 15 cc colloidal aluminum hydroxide plus 4 cc milk of magnesia (*5*) The patient s fasting gastric juice was removed and adjusted to pH 1 5 after which 35 cc was returned to the stomach as the control specimen This specimen was circulated around the electrode by the pumping system and a control tracing was made on the recording potentiometer

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John J Romano[3] (Albany Med College) Five series of experiments were made on each animal during one year Each series consisted of a week of control observation followed by a week of observations during which each animal received aluminum hydroxide gel by stomach tube three times daily for five days followed by a week of control observation

Averages of data from three consecutive days during the week of aluminum hydroxide gel feeding were compared with similar averages of the preceding control week In both animals during the first two series there were significant increases in volume, total chloride and free acid with less clearcut increases in total base In the remaining three series neither animal showed significant changes from the control except that in one dog in one series free acid appeared markedly increased No consistent shift in secretory activity to an earlier period of the day was evident as was seen with sodium bicarbonate In general these experiments indicate that aluminum hydroxide gel in moderate dosage has no significant effect on amount of gastric secretion

Photoelectric Method for Determination of Peptic Activity in Gastric Juice Benjamin C Riggs and William C Stadie (Univ of Pennsylvania) describe a method for estimation of peptic activity which combines rapidity with accuracy and is particularly adapted to clinical studies

Enzyme activity is measured photoelectrically as the decrease in turbidity of a standardized homogenized suspension of coagulated egg white under specified conditions Accurate measurement is possible down to a level equivalent to 1 gamma of crystalline pepsin Protein so measured follows a monomolecular course and hence the enzyme activity is expressed as a velocity constant The velocity constant is a curvilinear function of pepsin concentration and serves throughout the range encountered clinically as a convenient measure of the peptic activity of gastric samples

(3) Am J Phy I 141 255 58 Ap 1, 1944
(4) J Biol Chem 150 463 4 0 Oct b 1943

Five cc of the gastric contents is mixed with an equal volume of digestor and placed in a water bath at 37 C for 30 minutes with occasional shaking Hydrochloric acid solution is added drop by drop and shaken until the indicator denotes approximate neutrality If flocculation does not occur in less than five minutes after shaking for 30 seconds 0 2 cc ferric chloride solution is added with more shaking The flocculated sample is centrifuged for five minutes at top speed to pack the precipitate Uniform smears are prepared on glass slides dried in air fixed by heat and stained by Ziehl Neelsen s method

To prevent false positive reports tubes must be thoroughly washed with hot water and soap and then attached to a special water tap and water run through them for 30 minutes They are boiled for 30 minutes in a weak solution of sodium carbonate and finally placed on ice overnight

Guinea pig inoculation of gastric contents is a more delicate test and yields a higher percentage of positive results than direct microscopy

[The reliability of this procedure is verified by other investigators and should be resorted to more frequently when the indications exist —Ed]

Gastric Digestive Secretions in Infancy and Childhood are discussed by Irving J Wolman (U S Pub Health Service Hosp Sheepshead Bay N Y) Human gastric juice appears to contain no true rennin its milk-clotting power being due to the pepsin content Pepsin is present in indeterminate amount it is questionable whether the pH drops low enough during infancy for its proteolytic action to be effective Attention is directed to a newly discovered digestive enzyme cathepsin which appears to be of importance in protein digestion during early childhood especially and to the minor ferments lipase lipokinase gelatinase Brucke pepsin and the amylase activating factor The secretion of hydrochloric acid is low in infancy and increases with growth In the immediate neonatal period acid secretion is temporarily increased The fasting gastric secretion is an undependable index of acid secretory power Carbohydrate meals of the Ewald type are moderate stimuli alcohol is somewhat stronger and histamine provokes an excessive and unphysiologic response Few cases are recorded in which children with

( ) Am. J M S 0 (0 94 Dec mb 1943

the various substances were then added in 200 cc volume

Addition of calcium carbonate to milk enhances buffering properties of the milk which in turn prevents the calcium carbonate from causing an excessive rise in pH. The prolonged effect of the combination would also make unnecessary the repeated administration of milk alone. Similarly the combination of milk of magnesia and colloidal aluminum hydroxide gives more prolonged effect than colloidal aluminum hydroxide alone with subsequent need for smaller and less frequent doses. The undesirable initial rise in pH resulting from use of milk of magnesia alone is avoided and the constipating effect of aluminum hydroxide is offset. Milk of magnesia content may be varied from 4 to 15 cc without raising the pH of the mixture above 7.5, enabling adjustment for any desired laxative action. This mixture has been used clinically with excellent results.

Value of Examination of Gastric Contents for Tubercle Bacilli cannot be overemphasized according to John A. Foley and John F. Andosca (Boston Univ.). In a series of 639 cases in which tubercle bacilli could not be obtained in preparations stained directly or by concentration methods, gastric lavage disclosed bacilli in 187 (29.2 per cent); no positive result was obtained in 32 nontuberculous patients used as controls. Because of its reliability and definiteness, gastric lavage is justifiable in any patient suspected of having pulmonary tuberculosis. It is of therapeutic importance when it is necessary to decide whether active treatment such as collapse therapy should be started, and it is helpful in evaluating pneumothorax treatment.

TECHNIC.—Gastric contents are obtained in the early morning before ingestion of any food. A Levine tube is passed nasally into the stomach and with a Luer syringe 30–50 cc of gastric contents is aspirated. The reagents used are: (1) digestor—1 per cent sodium hydroxide containing 0.2 per cent potassium alum and 0.002 per cent bromthymol blue; (2) hydrochloric acid approximately 2.5 N (25 per cent concentrated hydrochloric acid by volume); (3) ferric chloride solution (1 per cent ferric chloride in distilled water);

(1) Ann. Int. Med. 19 6 96 3 October 1943

and exhaustion of germinal epithelium may occur This is evident in the atrophy and disappearance of glands and diminution in mucous secretion or metaplasia of surface epithelium and gastric pits Hypertrophic gastritis is considered to be a mechanical alteration in gastric mucosa but atrophic gastritis is an integral and late stage of chronic gastritis

Symptomatology of peptic ulcer may be present in the absence of a grossly demonstrable lesion but can be explained on a basis of chronic gastritis The apparent



Fig 105 (l ft) —S p fi l l l m t d b m l m co
Fig 106 (ght) —Alm t h led m al l w th m ou pl g

greater frequency of duodenal over gastric peptic ulcers may be due to the fact that minimal lesions can more readily produce a recognizable deformity in the duodenal wall

Hypertrophic Pyloric Stenosis in Adults Howard Wakefield (Northwestern Univ) states that evidence is accumulating to indicate that in some cases symptoms of hypertrophic pyloric stenosis of infancy continue into adult life before they produce a serious problem Clinical history and pathologic findings favor congenital origin In some

(9) G t t l gy 250 257 Ap l 1944

apparent anacidity have failed to produce free acid in repeated tests with histamine Many children with anemia have transient anacidity unless stimulated by histamine but the deficiency tends to clear as the anemia is corrected However there may be rare instances of anemia with complete or true anacidity in which acid is consistently absent With healthy children the range of values for acid production is so broad regardless of the stimulus used that the results of gastric analyses in disease conditions are almost always worthless

Peptic Ulcer and Chronic Gastritis The term chronic gastritis is applied by Vincent P Collins (Columbia Univ) to a pathologic process stemming from normal de generation and repair of gastric glands It differs from callous peptic ulcer only in degree The lesions may pene trate only partly through the muscle coat or only into the submucosa They are attended by a commensurate degree of fibrosis and granulomatous reaction and heal with minor scarring of the muscle coat and submucosa and some dis tortion of the mucosal elements In microscopic prepara tions these are limited by the muscularis mucosae and covered by a thin zone of fibrinopurulent exudate and granulation tissue The underlying submucosa shows some edema and a slight increase in fibrous tissue Adjacent mucosa flows into the defect so that the gastric pits and glands are directed into the defect and lie at right angles to their former position (Figs 105 and 106) A mucous plug is commonly seen to fill the defect

The imprint of this process can be recognized to some degree in every surgically resected stomach Evidence suggesting a similar process has been encountered in the duodenum The peptic ulcer as a lesion of gastric or duo denal mucosa is not a distinct entity but only the most obvious manifestation of chronic gastritis as here de fined It results when degeneration and necrosis are over whelming and the repair mechanism is inadequate When foci of degeneration and necrosis occur and recur in great numbers a prolonged proliferative resp [illegible] d forth

(8) Ann. S g 118 1005 1014 Decembe 194

cult and usually missed the condition often being mistaken for carcinoma of the outlet of the stomach. The most important feature in diagnosis is long history of nausea and vomiting plus roentgen evidence of the long pyloric canal described by Kirklin. Histologic examination of the excised mass is essential. Wakefield reports a case

Man 52 had had nausea and vomiting for 30 years. Childhood history was not clear. Nausea was nearly always present one half hour after each meal. Vomiting was frequent. He had no pain in the epigastrium or periodic symptoms of ulcer. Milk cream or antacids never afforded relief. Certain foods such as onions yellow turnips milk and cream cucumbers cabbage cauliflower and corn almost always caused vomiting. Roentgen studies in 1930 revealed a stenotic lesion at the stomach outlet but operation was refused. In 1932 the same lesion was revealed roentgenologically (Fig 107). He was still in fairly good health; there was no weight loss, appetite was good and blood and urine were normal. The lesion was resected and proved to be a muscle tumor 0 6 cm thick (Fig 108). At 64 the patient is in good health and able to eat anything.



Fig 108—Re t l l t t on h w hyp t phy f

[Such cases are more common than generally supposed. Occasionally symptoms are conspicuous by their absence. Many are mistakenly regarded as cancer or scirrhous carcinoma of the pylorus and are submitted to extensive resection. Naturally the possibility of carcinoma deserves first consideration in differential diagnosis.—Ed.]

cases the condition is compatible with a normal life ex pectancy Most ca es occur in males (perhaps over 80 per cent) about the same ratio as is found in infants The

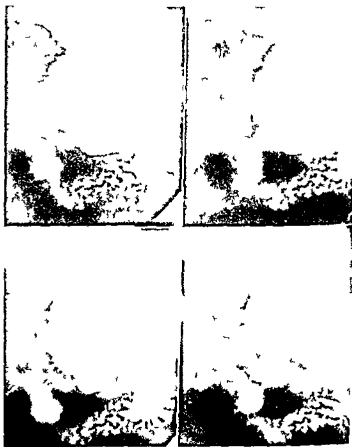


Fig 10

condition is probably more common than generally thought and should be considered in differential diagnosis of any stenotic lesion at the pylorus Nausea and vomiting of many years duration often dating back to childhood and infancy are the outstanding symptoms Diagnosis is diffi

administration of oxygen preferably by mask during the critical postoperative period intelligent administration of fluids and the early recognition and treatment of hypoproteinemia and vitamin deficiencies

[This article is largely of a surgical nature From a clinical diagnostic standpoint the contributions by the late Harry Singer on the basis of a rich and varied experience leave nothing to be desired —Ed]

***Giant Ulcer of Duodenum** is described by Samuel C Kahlstrom*[2]

Man 48 was hospitalized for hypertensive cardiorenal vascular disease About six months later he persistently complained of pain and tenderness in the right upper quadrant there were some weight loss and passage of tarry stools Stomach and duodenum appeared normal roentgenologically The course was slowly and progressively downhill and he had repeated severe gastric hemorrhages with profound shock a few months later He died of bronchopneumonia At autopsy the first 8 mm of the duodenum presented normal mucosa beyond this the entire posterior wall of the duodenal bulb was replaced by a huge ulcer 5 × 4 cm Most of the base of the ulcer was formed by the pancreas edges were well sealed preventing soilage of the peritoneum A large partially eroded vessel was present at the edge of the base and there was considerable induration suggesting chronicity Mucosal folds adjacent to the crater were not remarkable they did not radiate toward the ulcer Microscopic examination showed only chronic inflammatory cells around the ulceration

Only 10 duodenal ulcers larger than 1 cm have been reported and this apparently is the largest The lesion apparently was overlooked in roentgen examination because of its great size and absence of the usual deformity observed with duodenal ulcers Only 4 of the 10 lesions reported were recognized before operation or autopsy

It has been suggested that these giant ulcers may grossly resemble a normal or slightly abnormal cap and that the usual radiating arrangement of mucosal folds is not present In some cases the crater produced a diverticulum like structure Helpful differential points are narrowing of the duodenum beyond the ulcer by spasm or fibrosis absence of a connecting stem with the remaining duodenal

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(2) M B II V t Adm 0 451 45 J y 1944

Acute Gastroduodenal Perforations As the factors causing peptic ulcer continue to act the depth of the ulcer increases and perforation is facilitated When intragastric exceeds intra abdominal pressure perforation occurs in gestion of a heavy meal or liquids or sudden straining or lifting may precipitate this complication According to Edward J McCabe and Walter L Mersheimer[1] (New York Med College) perforation should be diagnosed without difficulty in most cases 75 per cent of them pre senting a suggestive or definite history of ulcer Sudden onset of the illness and severity of the pain with rapid spread throughout the abdomen and perhaps to one or both shoulders frequently suggest the diagnosis Out standing physical signs are the boardlike rigidity of the abdomen and its silence to auscultation Diminution of liver dulness and roentgen evidence of pneumoperitoneum are pathognomonic for a ruptured viscus recovery by peritoneal aspiration of ingested dye solution is pathog nomonic for ruptured gastro intestinal tract When diag nosis cannot be confirmed by these signs serum amylase should be determined to exclude the possibility of acute pancreatitis

When laparotomy is decided on the patient should be given intravenous fluids preoperatively if necessary to combat shock or dehydration Morphine should be given freely The stomach should be emptied by preoperative gastric extraction by nasogastric tube and by Wangensteen suction continued through the operative and postoperative phases Spinal anesthesia facilitates operation A small high incision should be used and simple plication rein forced with omentum should be the only procedure in most cases When perforation has been present over six hours intraperitoneal application of sulfonamides is man datory Extreme care must be used in closing the inci sion Retention sutures should be used and steel alloy sutures can be used advantageously Postoperative care should emphasize avoidance of gastric dilatation by con tinuous gastric suction prevention of anoxia by routine

(1) Am J Surg 6 39 49 Oct 1943

administration of oxygen preferably by mask during the critical postoperative period intelligent administration of fluids and the early recognition and treatment of hypoproteinemia and vitamin deficiencies

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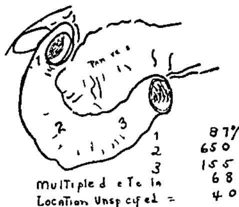
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bulb in diverticuloid lesions and overlying tenderness In Kahlstrom s case only the last was present Re examination of roentgenograms after autopsy did not disclose any evidence to warrant diagnosis of ulcer or any other abnormality

[This article is of interest for the literature occasionally cite other ca es of a similar nature Among the many thousand of duodenal ulcers that I have seen I do not recall one of the giant variety and at the moment I am not familiar with any surgical or pathologic observations anent such giant ulcer on the part of my colleagues —Ed]

Duodenal Diverticula Following a study of 103 cases of duodenal diverticula Harry A Warren (Champaign Ill) and Edward S Emery Jr (Harvard Univ) concluded that this condition is associated with no typical



Fg 109—I c t n of d ode l d tic la

symptomatology Figure 109 illustrates the location of the e duodenal diverticula Those found in the first portion of the duodenum are usually of the false type and appear to be associated in most instances with duodenal ulceration Those in the second portion are usually a true herniation of the mucosa through the muscular wall A fair number of the e show inclusions of pancreatic tissue Four cases showed evidence of inflammation in the sac One patient with a localized abscess died of purulent meningitis hepa

(3) Ca t or t l gy 1 1085 109 D mbe 19

tins and endocarditis In general the smaller pockets are less likely to be of clinical importance than the larger ones

Pain in the Abdominal Wall is di cu ed in an editorial by Kobert Elman The importance of abdominal pain pro duced by the intercostal nerves or the vertebral column has been emphasized and a variety of terms used to desig nate the condition One of them is inter ostal neuralgia or neuritis another is neuralgia of the abdominal wall In many instances tructural change in the vertebral column tumors of the spinal cord faulty posture or sacro iliac or lumbar sprain may be present Failure to recog nize such a mechanism leads not only to unneces ary oper ations but more important to recurrence of the same pain after such procedures

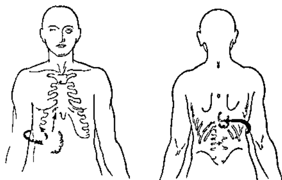
Recognition of abdominal wall pain originating in the thoracic nerves or vertebral column requires merely that the physician s mind be prepared for such diagnosis Once suspected diagnosis is usually not difficult The tender ness is definitely located in the abdominal wall and may be sharply localized to the rectus or other abdominal muscle a finding which requires only careful palpation There is often a definite correlation between movement of the vertebral column and development of pain so that the clinical picture in many instances is characteristic of lumbago the patient having great difficulty in getting into a comfortable position when lying particularly at night Finally although significant gastro intestinal disturbance such as nausea or vomiting is seldom associated with the abdominal pain these symptom are occasionally also found

Treatment when effective often adds to security of the diagnosis Relief is often obtained by efficient immobiliza tion of the sacro iliac or lumbosacral joint with strapping Use of a rigid bed frequently brings relief In many cases reassurance is all that is needed for symptoms often dis appear as suddenly as they appear Orthopedic manipu lations may be indicated

(4) C t oe ter l gy 1 974 975 O t b 1943

Back Pain in Disease of Gastro Intestinal and Accessory Gastro Intestinal Tract. Andrew B Rivers and Andries I Roodenburg (Mayo Clinic) suggest that back pain as one of the manifestations of gastro intestinal disease can result from a summation of impulses originating in visceral walls and referred to the back along the sympathetic nerves which carry such impulses to the cord

Unilateral shifts of pain arising because of penetrating lesions involving these tracts can and probably often do travel to the cord along branches of the spinal nerves



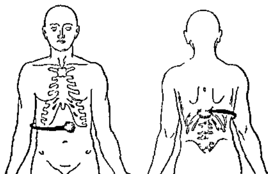
Fg 110—D t b t f p n prod ced by d od nal ulcer

This is a slightly different type of pain from that usually caused by impulses arising within visceral walls being more acute more localizable and better limited to definite segmental distributions Figure 110 shows the distribution caused by duodenal ulcer Shading left indicates region where pain is felt most frequently and arrows indicate directions of shift into secondary regions Shading right indicates most frequent location of back pain in extensive or penetrating duodenal ulcer Location of pain in a case of carcinoma of the pancreas is shown in Figure 111 pain originated in shaded area on left and was referred to shaded area on right

In inflammatory and occasionally in erosive neoplastic disease involving retroperitoneal tissues such as acute

(5) J A M A 125 421 426 J e 10 1944

pancreatitis back pain is an important symptom Lesions in this region could involve both spinal nerves and those using sympathetic routes pain is deep seated frequently severe and fairly well localized A characteristic feature of this pain often of diagnostic importance is that patients with such lesions usually lean forward to relieve the pain Malignant lesions originating in the gastro intestinal tracts may metastasize to the spinal column the pain is usually boring deeply located bilaterally felt and constant In most instances back pain as a manifestation of the diges



Fg 111—Locat on f p p od d by noma f p ea

tive or accessory digestive tract is a symptom to be considered carefully because usually it indicates that the lesion causing it is complicated It is always well to suspect disease arising in the gastro intestinal or accessory gastro intestinal tract when dyspepsia is associated with back pain

Gastro-Intestinal Disturbances in the Combat Area Alexander Ru h (M C A U S) presents preliminary observations on peptic ulcer In a large hospital in the South Pacific peptic ulcer was diagno ed in slightly over 1 per cent of all medical patients admitted during a 12 month period Approximately half of the ulcer patients gave clearcut histories of previous attacks and a typical and classic history was obtained from 80 per cent the

(6) J A M A 1 3 389 391 O t 16 1943

history was misleading in the remaining 20 per cent Sixty per cent of the patients had epigastric tenderness which in one fourth of these was unmistakable No relation however could be established between type and locality of lesion and character of the pain and tenderness Sixty seven per cent of the diagnoses were supported by x ray evidence A crater was demonstrated in only 21 per cent of the patients with positive x ray signs This figure differs widely from those of some gastro-enterologic services in large civilian hospitals where direct x ray evidence is said to be obtainable in approximately 95 per cent This difference may be ascribed to technical difficulties in the field and to the fact that patients are examined before the pathologic process has become extensive

Analysis of gastric contents and examination of stool for occult blood are of limited value but the acid test described by Palmer and the relief following continuous alkaline milk drip therapy have been useful adjuncts in establishing diagnosis

The soldier with a peptic ulcer should be removed from the combat area as soon as practicable after diagnosis

Gastro Intestinal Disturbances in the Combat Area Preliminary Observations on Functional Disorders of the Digestive Tract Alexander Rush[7] (M C U S A) found that patients with functional disorders of the gastro intestinal tract constituted 53 per cent of 200 admitted because of dyspepsia to a large hospital in the forward area The characteristic complaint is distress induced by ingestion of food The scores of the army general classification tests give striking confirmation to the clinical impression that most of these patients are incapable of adapting themselves to field service and are poor risks in the combat area For the most part the response of these patients to therapeutic measures in the field is transient and poor Patients who are shown to be poor learners and who persistently fail to make any satisfactory improvement should be returned promptly to the zone of the interior for reclassification

(7) J A M A 1 3 4 1473 O t 3 1

Military Gastro Enterology J W Annis and Franklin G Eldridge (M C A U S) present a survey of the gastro intestinal section of an army station hospital during mobilization and under wartime conditions In two years there were 3 012 visits to the outpatient gastro intestinal clinic Many patients including all those with peptic ulcer or gastritis were later hospitalized 2 615 roentgen studies were made on 2 359 patients

Incidence of peptic ulcer in this series did not vary greatly from that seen in civilian life the ratio of duodenal to gastric ulcer was approximately 15 1 The authors base their belief that the neurogenic factor in peptic ulcer is a major and in most cases the most important single factor involved on (1) frequency with which emotional upset precipitates activity of the ulcer (2) tendency toward occurrence in nervous and high strung individuals and (3) prompt response to rest and sedation Immediate discharge of any patient with peptic ulcer is in the best interests of patient and government There may be rare exceptions if the person is a highly trained specialist or for any reason virtually irreplaceable If such a person can follow a carefully controlled regimen in the Army he may be allowed to remain

The military problem presented by patients with ailments classified as functional dyspepsia calls for the greatest acumen and judgment by the medical officer Many men with transient problems of adjustment and resulting vague gastro intestinal complaints are readily rehabilitated into useful soldiers Constitutionally inadequate persons are of no military use and should be rejected or discharged as rapidly as possible They do not do well even in limited service but invariably break down at crucial moments Troops both at home and abroad are infinitely better off with an inadequate number of reliable men than at full strength partially comprised of undependable cardboard soldiers A small intermediary group exists and decision in these cases is extremely difficult it often can be made only after prolonged observation and repeated trials at

(8) South M J 36 91 95 Dec mb 1943

various duties It is better to err on the side of leniency and in doubt to return these men to civilian life Frank malingering is also frequent and substantiation difficult Besides obvious cases *there are many less clearly defined* which merge with true psychoneurosis None of these men have any potential military worth Regarding functional dyspepsia as a whole the Army provides neither time environment nor facilities necessary to attempt the extremely difficult and often unsuccessful task of rehabilitation

Management of Ulcers among Naval Personnel Waltman Walters and Hugh R Butt (M C U S N R) state that peptic ulcer offers a difficult problem in the naval service especially aboard ships New recruits with uncomplicated ulcer which was present before enlistment are mostly young and few should be considered candidate for surgery It is advisable to discharge them from the service before the government becomes responsible for their continuous treatment and disability pensions

The *situation is different with officers and enl*sted men whose ulcers have developed in the service There seem to be an impression that if they are operated on most of them will have to be assigned to limited duty But the authors believe that a large number can be returned to full active duty if operation preferably partial gastrectomy is performed as soon as diagnosis is established Therefore they have operated on 13 such patients in the past six months and 11 have returned to active duty

Reports from 13 United States naval hospitals show that 1 352 patients with proved peptic ulcer were admitted from Dec 1 1940 to Dec 1 1942 and that 1 249 were treated medically and 103 surgically 55 per cent of the former and 71 per cent of the latter were returned to duty (53 to active and 20 to limited duty) Of 63 patients who had had previous operations for ulcer 25 per cent underwent another operation for recurrence with or without obstruction and 75 per cent were treated *medically* 38 per cent of the 63 were returned to duty

(9) A S g 118 489-498 O t be 1943

The importance of making an early decision as to the type of treatment to be used and the dispo ition of the patient cannot be overemphasized Of the 13 patients oper ated on by the authors only 2 were invalided from the service One was an officer who had spent 14 months in various hospitals undergoing courses of medical treatment before operation wa advi ed Although the surgical re sult was excellent the long period away from duty and the mental attitude developed by prolonged hospitaliza tion and limitation of activities produced a functional failure in two months after return to duty The other patient also had a good surgical result but was discharged for an incapacitating war injury

From the results obtained there is justification for radi cal surgical treatment of naval patients who have chronic recurring gastric or duodenal ulcers which develop dur ing service Officers and enlisted specialists with such ulcers whose knowledge experience and ability make them particularly valuable to the navy and the 25 per cent of medically treated patients who are discharged from the service because of chronic recurring ulcers are the par ticular patients who should be given the benefits of sur gical treatment with the hope that their valuable services can be retained However until a much larger series is operated on and observed subsequently as regards reaction to naval duty the advisability of surgical treatment to return patients to duty cannot be determined definitely

[With few exceptions the difficulties of diagno is treatment and d position do not differ from those of our Briti h and Canadian allies, judging from the numerous published reports There are many authorities who would honestly differ with the author w th re pect to the indicat on or justificat on for ga tric re ection under the circumstances Certainly it should be under taken only as a last resort Of course n the hand of uch an expert as Walters the operat on is carried out with surprisingly low surgical mortality and po tope ative morbidity but a danger ous precedent might be e tabli hed if such operations were car r ed out on an extensive cale —Ed]

Disease in the Canadian Army during World War II

According to H A DesBrisay the most prevalent di order among Canadian military per onnel i dyspepsia

(1) B R V o M A 1 6 8 J ly 1945

usually of the functional or reflex type Emotional tensions generated by the war apparently are appearing as psychosomatic disorders Reactions from resentment and frustration are important in engendering dyspepsia and reactivating ulcer The incidence of peptic ulcer is greater than in the last war the heightened tension consequent on mobile mechanized warfare added to defects in diet long periods between meals focal infection mental strain and worry familial tendency and excessive smoking is believed to be responsible

Gastric neurosis is also significant Most of these patients have a history of nervousness or breakdown War induced neuroses have been few but proportionately more frequent among service men than among civilians While most of the neurotics should not have been accepted for service many of them might not have broken down had they been exposed to battle stress for morale is awareness of efficiency and efficient performance cannot be maintained at a high level if the individual is held back

Typhoid fever is practically nonexistent in this war Dysentery was practically universal in the Libyan campaign but better control is expected from the use of antidysenteric serum sulfaguanidine and succinylsulfathiazole Catarrhal jaundice which has appeared in epidemic proportions in England may respond to convalescent serum

Peptic Ulcer Treated with Aid of Posterior Pituitary Extract M Hill Metz and Robert W Lackey (Baylor Univ) report satisfactory clinical results in 311 of 418 unselected cases Of this series 200 were personal patients and 218 were treated by physicians from all parts of the United States

In only 8 of the 200 personal cases was bed rest instituted at onset of treatment The diet consisted of three meals daily with milk once between meals and at bed time The diet satisfied all protein mineral and vitamin requirements and omitted only the obvious irritants and most indigestible foods such as fried ones coarse vegetables and some pastries Along with posterior pituitary

( ) South M J 36 747 50 November 1943

extract the patients were regularly given an effective antacid and an antispasmodic such as atropine both for about the first two weeks of care

Intranasal insufflation of desiccated posterior pituitary powder is the most dependable means of administration With a small nasal insufflator the patient blows 2/3 gr powder a little at a time onto the upper nasal mucous membranes By this route the agent s action is slow and continuous It is taken about one hour after each meal *and at bedtime (2 2/3 gr daily) This dose is continued* for six to eight weeks and then cut in half for two weeks more

The hormone should be considered a supplement to the rational medical management of uncomplicated peptic ulcer Experimental data show the possible relationship of the posterior pituitary body to gastroduodenal ulcer and also the action of the extract in successful treatment of this syndrome

Peptic Ulcer, an Endocrine Disease Sixteen years ago John A Crabb (Topeka) began using parathyroid ex tract and found that acute subacute and most chronic peptic ulcers heal promptly Evidently there are chronic cases with scar tissue obstructing the pylorus in which operation is the only solution In others a dense ring of scar tissue may prevent an adequate blood supply to the ulcer and thereby retard or prevent healing

During the first few years there were several recur rences 12–18 months after treatment was discontinued but they yielded promptly to treatment Later since he has advised his patients to come for a small dose of hormone every two or three months he has had few recurrences

The usual treatment with variations to suit individual cases consists of 1 cc parathyroid extract every third day for three doses then 10 minims every five to seven days for 6–12 doses *as seems necessary from the results* obtained

A palliative is also used such as a bismuth and pare goric mixture or an alkaline powder to be taken 20–30

(3) J Kansas M Soc 41 368 374 November 1943

minutes before the expected pain for the purpose of neutralizing the hydrochloric acid and to coat over and temporarily protect the ulcer from the eroding gastric juice. It is not advisable to give alkalines immediately after meals at any time they make pepsin inert and interfere with or prevent proper digestion of proteins

The diet is restricted to liquids or nourishing nonirritating soft foods for a few days then gradually increased in variety and quantity Food is given for nourishment and not with the object of causing the ulcer to heal Some of the foods allowed are milk cream cereals milk toast meat juices soft eggs custards and others which the resourceful doctor may select

Crabb is convinced that peptic ulcer is an endocrine disease and is caused by and fails to heal because of a lack of parathyroid hormone in the system Replacement therapy is used on the same principle as the use of liver hormone in pernicious anemia or of thyroid hormone in cretinism or myxedema In these conditions the hormone must be replaced at intervals to maintain normal balance and function or there will be recurrence Peptic ulcers also recur and the recurrence is amenable to parathyroid hormone therapy Other treatments are strictly palliative

[The two foregoing articles are examples of the divergent views held with respect to the genesis and therapy of a disorder concerning which definite knowledge is still lacking —Ed.]

Prompt Feeding Program for Bleeding Gastric and Duodenal Ulcer Edwin A Rasberry Jr and T Grier Miller[4] (Univ of Pennsylvania) analyze 2 111 cases of grossly bleeding gastric and duodenal ulcer all treated by the prompt and frequent feeding program This series shows gross mortality of 4 per cent and net or corrected mortality of 1 9 per cent It indicates that except when coincident perforation has occurred better results both as to survival of patient and as to his comfort during illness are obtained by this regimen than by any other form of conservative treatment or by surgical intervention

Treatment of Bleeding Peptic Ulcer Leon Schiff[5]

(4) C t oent d g 1 911 921 Oct b 1943
(5) South M J 37 335 34 J e 1944

(Univ of Cincinnati) reports on 160 patients treated by a prompt feeding program with a slightly modified Meulengracht diet Diagnosis of ulcer was confirmed in each instance by roentgen examination gastroscopy operation or autopsy Proportion of males to females was about 7 1 and 89 of the patients were 50 or over In 12 there was no history of any digestive distress prior to hemorrhage and in 33 the digestive symptoms were not typical of peptic ulcer Approximately half the patients had had no previous hemorrhage while a little over one fourth had had one or more previous bouts of bleeding In 121 bleeding was severe enough to reduce the erythrocyte count to 3 000 000 or less and in 61 to 2 000 000 or less

Eighty one patients received one or more blood transfusions usually consisting of 500 cc citrated blood Gross mortality was 6 8 per cent a considerable improvement over 25 6 per cent resulting with the starvation regimen practiced between 1927 and 1937 Average hospital stay was *25 6* days in contrast with *32 4* days with previous treatment Death resulted from exsanguination in 3 1 per cent and in others from complicating factors In 8 of 11 fatal cases death occurred during the first episode of bleeding

General principles of treatment consist of (1) rest and reassurance (2) sedation with avoidance of morphine if possible (3) oral administration of fluids supplemented if necessary by hypodermoclysis or intravenous drip (4) blood transfusion (5) no enemas before the sixth day except in presence of rectal discomfort or fecal impaction and no laxatives except mineral oil after the first week (6) alkalis only in presence of pain (7) ferrous sulfate 5 gr three times daily preferably after cessation of tarry stools (8) prompt feeding of a diet consisting of milk cream butter eggs strained cereals puddings pureed vegetables and fruits ground scraped or minced meat white bread plain or toasted and weak tea or cocoa with feeding at two hour intervals from 8 00 a m to 8 00 p m (9) surgical treatment if medical m fails to control the bleeding

Prompt feeding is justified for several reasons With holding food and drink does not rest the stomach for strongest peristaltic waves occur when the stomach is empty There is marked shortening of clotting time during absorption of mixed meals due only to the protein fraction of foods Patients started on the regime in 24–48 hours are much more likely to bleed again than patients fed at once Exhausted patients die after hemorrhage despite scrupulous dieting Patients with protracted hemorrhage sometimes stop bleeding when they receive food Ambulant patients frequently recover from severe melena without making any change in diet Presence of food in the stomach increases its tone and the stomach maintains a constant and continuous pressure on its contents tending to close an open vessel and promoting clot formation Regeneration of blood occurs much more rapidly with administration of food Clinical experience with prompt feeding shows that convalescence is shortened and mortality reduced

[The advocacy of a prompt feeding program by such experienced clinicians as Schiff and Grier Miller is in accord with the current teaching with few exceptions Our case records are replete with instances of moderate to fairly severe gastroenteric hemorrhage despite which the patients continued to eat and carry on as usual without any serious effect Contrariwise those undergoing conventional treatment in a hospital recovered more slowly as a rule and also sacrificed considerably more work hours However in instances of massive exsanguinating hemorrhage such prompt generous feeding may prove unwise in my judgment In such instances an individualized form of treatment is essential —Ed]

Alkalosis in Antacid Therapy Walter I Palmer in an editorial reviews studies which deal systematically with the four main aspects of the mechanism of development of alkalosis in antacid therapy and indicate effective means for its prevention These aspects are (1) effect of a soluble alkali such as sodium bicarbonate (2) effect of relatively insoluble alkalis such as calcium carbonate (3) role of chloride loss and (4) role of the kidney

The alkalosis induced by soluble alkali is characterized by an increase in the pH and the sodium total base and

(6) Ca troe terology 1 89 893 S ptember

bicarbonate content of the blood This type of alkalosis does not develop if renal function is normal and if the amount of water supplied daily is sufficient to eliminate the base as rapidly as it is absorbed No conclusive evidence has been obtained to indicate that calcium carbonate per se produces alkalosis Large amounts of aluminum hydroxide or aluminum phosphate likewise do not alter the electrolyte constitution of the blood plasma The alkalosis observed during administration of calcium carbonate is identical with that seen in patients with pyloric obstruction It is attributable entirely to the chloride loss resulting from gastric aspiration or emesis together with an inadequate salt intake It can be prevented by administration of sufficient amounts of sodium chloride despite continued use of calcium carbonate Chemically the alkalosis is characterized by a decrease in the serum chloride sodium and total base and by an elevation in the pH and bicarbonate content of the blood

Although a decrease in urea clearance is noted frequently during alkalosis renal function invariably returns to its original level after the acid base balance is restored Similarly no permanent decrease in urea clearance results from long-continued administration of alkali Azotemia and impairment of renal function do not occur during alkalosis of hypochloremia if the supply of water is adequate It is apparent therefore that the alterations in renal function are by products of the alkalosis and do not operate in its production Significantly the prolonged use of alkali with or without alkalosis does not produce detectable anatomic changes in the kidney of the dog or man when water intake is not limited Prolonged depletion of chloride however may lead occasionally to a deposition of calcium in the renal collecting tubules attributable to an alteration in the physical state of the urine

The alkalosis complicating the Sippy treatment is thus attributable to (1) absorption of sodium bicarbonate (2) loss of gastric chloride or (3) a combination of the two As sodium bicarbonate is no longer routinely used in ulcer therapy chloride loss constitutes the chief cause of

the disturbance An adequate intake of salt obviously will eliminate alkalosis as a complication of antacid therapy the amount required depending on the amount of chloride lost Some salt may be added to the diet However if the body chlorides are depleted if vomiting is present or if the quantity of gastric content aspirated is considerable additional salt will be required usually 5–10 Gm by mouth daily or in acute disturbances 15–50 Gm intravenously as normal or hypertonic saline The important point however is that the alkalosis is not the result of the antacid administered or of renal injury or impaired renal function it is purely the result of chloride depletion

Effect in Vitro of Various Detergents on Peptic Activity of Human Gastric Content. Joseph B Kirsner and Regis A Wolff (Univ of Chicago) report experiments in which increasing amounts from 25 to 150 mg of various detergents and of chemically pure octyl decyl dodecyl tetradecyl and octadecyl derivatives of the alkyl sulfate series were added to 5 cc samples of human gastric juice The pH of samples was measured by the Beckman glass electrode Peptic activity was determined in duplicate by the Beazell modification of the Anson Mirsky method adapted for the Evelyn photo-electric colorimeter At least two experiments were performed with each compound

Zephiran a cationic detergent and Igepon AP Aerosol OT Intramine Daxad #11 Daxad #21 Daxad #23 and Arctic Syntex A all anionic detergents do not inhibit peptic activity of 5 cc human gastric content when added in amounts to 150 mg Tergitol 7 and Actival both anionic detergents decrease peptic activity moderately Duponol PC and Naccanol E both anionic detergents inhibit peptic activity markedly and as effectively as commercial sodium alkyl sulfate Among a homologous series of alkyl sulfates the decyl and dodecyl derivatives are most effective in lowering peptic activity of human gastric content

(7) Gastroenterology 2 0- 3 [illegible] 1944

Inhibition of Peptic Activity in Treatment of Peptic Ulcer was *studied by F Steigmann and Arthur R Marks*[8] (Cook County Hosp) A Rehfuss tube was introduced into the stomach of the fasting patient and the entire gastric contents were aspirated With the tube in place a test meal of four Uneeda crackers and 200 cc water was given and samples of gastric juice were aspirated every 15 minutes for two hours pH and peptic activity were determined on each specimen On succeeding days the patient received shortly after the test meal 1 or 2 capsules (100 mg) of sodium lauryl sulfate 2 Gm calcium carbonate 8 cc of an aluminum hydroxide preparation or 2 tablets of a magnesium hydroxide compound (6 gr magnesium hydroxide) Some patients received a repeat dose of sodium lauryl sulfate or magnesium hydroxide immediately after the fourth aspiration i e at hourly intervals Each patient was tested on five successive days To test the efficacy of sodium lauryl sulfate a similar group of patients received the usual ulcer diet plus 1 capsule of sodium lauryl sulfate every hour for 12 or more doses depending on symptoms Other antacid therapy was withheld but tincture of belladonna or phenobarbital was frequently given as supplementary medication

Calcium carbonate aluminum hydroxide magnesium hydroxide and sodium lauryl sulfate decreased peptic activity simultaneously with a rise in pH Calcium carbonate aluminum hydroxide and magnesium hydroxide caused more marked peptic inhibition than sodium lauryl sulfate The authors could not confirm reported observations that sodium lauryl sulfate inhibits peptic activity in the presence of an unaltered pH Clinical use of sodium lauryl sulfate on a small number of patients on the usual ulcer diet failed to reveal any superiority of this medication over some of the other medications used

[Discussions concerning the pathogenesis of gastric and duodenal ulcer chiefly emphasize the role of hydrochloric acid But actually the proteolytic effect of activated pepsin is of paramount

(8) Am. J Dig t D 11 173 178 J 1944

importance not only in the genesis but in the chronicity of such lesions Experimental and clinical observations in recent years have clearly demonstrated this fact Hence the rationale of anti peptic adjuvants to treatment To what extent such forms of therapy will be used remains to be seen As inactivation of pepsin is accomplished by adequate neutralization of gastric contents we still depend on such time honored procedure to prevent proteolysis and thus facilitate healing without resorting to those newer agents the efficacy of which apparently is till a matter of controversy —Ed]

Treatment of Gastroduodenal Ulcerative Disease with Sodium Alkyl Sulfate S J Fogelson and D E Shoch[3] (Northwestern Univ) present a preliminary report on experimental observations on dogs and clinical trial in 34 patients with ulcer who had not responded to previous therapy Sodium alkyl sulfate a surface active agent was well tolerated by patients who received 0 2 Gm every two hours during the day No toxic effects occurred in experimental animals or patients during seven months administration of this dose Survival time of dogs treated by the Wangensteen technic with massive daily doses of histamine was markedly prolonged by oral administration of sodium alkyl sulfate which inactivated pepsin in the stomach and did not alter the acidity

All patients treated were classified as having intractable ulcer by their physicians because their symptoms could not be controlled by any orthodox management including operation in six Symptoms of 26 were controlled by sodium alkyl sulfate and they were physically restored so that they were accepted by either the armed forces or industry 8 obtained no relief Two had recurrences on cessation of medication despite definite healing of the original lesions

The authors conclude that sodium alkyl sulfate is not a panacea for patients with ulcer It does not cure the patient who is subject to ulcers but will permit healing of some ulcers resistant to all other known types of management

Pepsin Inactivation in Ulcer Therapy A Morton Gill and C A Keele[1] believe that inactivation of pepsin is

(3) Arch Int Med 73 212 16 March 1944
(1) Brit M J 2 194 196 Aug 14 1943

the aim of peptic ulcer therapy and that this is obtained by neutralization of the gastric juice to pH 3 5–4 The effectiveness of the usual method of treatment by milk and antacids in fulfilling this aim is considered

As milk can neutralize an equal volume of 0 3 per cent hydrochloric acid to pH 4 the amount of milk in an ulcer diet would theoretically be governed by the total quantity of acid secreted daily provided the milk is given at the right times There are considerable individual variations in response to milk Data are presented regarding three ulcer patients to whom 10 oz milk was given every two hours In one of these almost continuous neutralization was secured but in the other two the values for free hydrochloric acid between feedings reached levels as high as 80 units Hourly feedings of 10 oz milk to a patient demonstrating this latter phenomenon resulted in more continuous neutralization but the optimal method appeared to be a continuous alkaline milk drip using 6 pt milk with sodium bicarbonate every 24 hours

Milk contains several substances which may influence gastric secretion Fat is probably the most powerful constituent It inhibits gastric movements and secretion when it reaches the duodenum and fatty acids are far more active than the fats from which they are derived The action of fats is due to liberation of enterogastrone in the intestinal mucosa this inhibits the movements and secretion of the stomach Sugars in high concentrations also inhibit gastric secretion and mobility Proteins act as buffering agents but some proteins can stimulate gastric secretion probably through their breakdown products

Thus the inhibitory effect of milk is due partly to depression of secretion and partly to neutralization and if given in quantities greater than 5 oz hourly milk is undoubtedly an efficient therapeutic neutralizing agent but in most cases something more will be required to raise the pH to 4

Antacids are almost invariably used to supplement the neutralizing action of milk Kirsner and Palmer and

Kirsner recorded the pH of aspirated gastric samples at hourly intervals in patients with healing duodenal ulcer given hourly feedings of milk and cream plus antacids hourly midway between the milk feedings The gastric contents were aspirated just before each feeding i e half an hour after the antacid was given They found that milk and cream feedings alone (3 oz total volume) had no effect after one hour although others have found that larger volumes or more frequent feedings were effective A general diet raised the pH somewhat

A number of antacids in various doses and atropine were tested Two Gm calcium carbonate hourly raised the pH from 1 75 to 4 35 2 Gm magnesium carbonate from pH 1 9 to 5 1 2 Gm magnesium trisilicate from pH 1 95 to 2 57 2 Gm tribasic calcium phosphate from pH 1 75 to 2 61 2 Gm tribasic magnesium phosphate from pH 1 65 to 3 06 and 30 cc aluminum hydroxide from pH 1 9 to 3 0 Atropine enhanced the action of calcium carbonate but had little effect on the other drugs

The order of efficiency of drugs acting alone in equal (2 Gm) doses was calcium carbonate magnesium carbonate tribasic magnesium phosphate tribasic calcium phosphate and magnesium trisilicate Thirty cc of 5 per cent colloidal aluminum hydroxide is probably little inferior to calcium and magnesium carbonates

It is unlikely that methods of treatment in which two hourly milk feedings are given with antacids halfway between would be as efficient in neutralizing free hydrochloric acid as the hourly administrations of Kirsner and Palmer so a pH of 4 will probably not be reached for very long and at night there will be no neutralization on either regime Since most peptic ulcers heal readily it may well be that complete inactivation of pepsin is unnecessary and that a pH of 2-3 will cause sufficient reduction of proteolytic activity This however is not definitely established and if an ulcer does not heal it is important to determine free hydrochloric acid or pH levels of gastric contents to see how much neutralization has occurred There are patients in whom [illegible] levels

increase when antacids are added to a two hourly milk feeding regime and such patients probably require continuous drips of milk or colloidal aluminum hydroxide to control free hydrochloric acid level adequately

Ulcer in Descending Duodenum Chauncey N Borman (Univ of Minnesota) reports seven cases diagnosed by

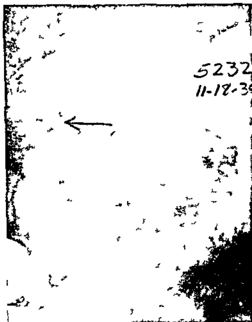


Fig 112 —Ul er ct t ppe d m l l bo d f d d g d od n m w th p m d m al h g dj t d d g d ode m

roentgen examination *In three instances location of the* crater was confirmed surgically In all seven cases the crater was located on the upper and inner margin of the descending duodenum usually just below the superior flexure (Fig 112) Secondary spasm mucosal distortion and medial retraction of the adjacent upper descending duodenum *occurred in every case Macroscopic hemor*

(2) Am. J R entgen 1 50 5 764 De embe 1943

rhage was prominent in six cases in three instances blood loss was unusually severe Nocturnal pain was present in four cases

Peptic ulcer rarely occurs in the descending duodenum (Fig 113) and its roentgen diagnosis is reported even less frequently Failure of the roentgenologist to explore

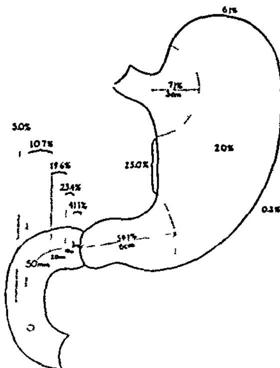


Fig 113—Topog aph c dist b t n of 196 g t c d 158 d odenal l s

this particular area of the duodenum thoroughly and failure to differentiate ulcer from the more common simple and pseudodiverticula partially account for the discrepancy

[Such low location of the ulcer is not as *infrequent* as is generally supposed. These ulcers may be overlooked in the routine roentgenoscopic *examination even by the most expert* by virtue of their *low location An illustration of this diff* ex

emplified by one of my most recent cases The patient gave a typical history of chronic peptic ulcer coupled with recurrent melena We were definitely of the opinion that he had a duodenal ulcer Gastroscopic examination was negative The surgeon who saw the patient in consultation suggested an x ray examination of the small bowel for the presence of a possible bleeding lesion presumably in the jejunum or ileum It was during this examination with the progress meal that the ulcerating lesion in the second portion of the duodenum was discovered Treatment as for ulcer promptly caused marked amelioration and subsequent disappearance of the symptoms Some authorities regard such ulcers as more refractory than those in the usual position in the proximal first inch of the duodenum —Ed]

DISEASES OF THE BILIARY TRACT AND PANCREATIC SYSTEM

Toxipathic and Trophopathic Hepatitis H P Himsworth and L E Glynn (London) produced two types of experimental hepatitis in rats toxipathic due to direct action of noxious substances on liver cells and trophopathic due to dietary deficiency of a component of protein Experimental toxipathic hepatitis develops rapidly after exposure to the poison with diffuse zonal necrosis In survivors recovery is complete repeated exposure to the poison however produces diffuse hepatic fibrosis Experimental trophopathic hepatitis develops only after a long latent period with massive necrosis leading always to postnecrotic scarring and in severe cases to nodular hyperplasia The relationship of this type of hepatitis to dietary protein deficiency is so definite that diets may be constructed that cause necrosis in 100 per cent of animals and by varying protein content the speed of development and severity of the lesion can be varied Both quality and quantity of protein are important suggesting that the protective factor is a component of protein rather than an intact protein molecule Casein even in small amount protects against the lesion while yeast protein even in liberal quantity fails to protect The protective power of various amino acids was tested and methionine in which casein is particularly rich gave complete protection

In man hepatitis following exposure to such poison as

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chloroform pho phorus and carbon tetrachloride has features characteristic of toxipathic hepatitis Zonal hepatitis seen with eclampsia and infective hepatitis and after treatment with organic arsenical preparations also appears to be of this type Association of two or more weak toxipathic agents may produce a high incidence of severe hepatitis Massive hepatic necrosis and its sequel nodular hyperplasia may be attributed to trophopathic hepatitis There is suggestive evidence that this can arise as the direct result of a dietary deficiency but most commonly it develops as a complication of a preceding illness and is then to be regarded as a conditioned deficiency disease distinct from the illness which it complicates Restriction of intrahepatic circulation is an important predisposing cause It most commonly results from swelling of liver cells previously injured by a toxipathic agent Pregnancy vomiting and anorexia contribute to its development by reducing the amount of protective nutriment available to liver cells Increased metabolic rate may have the same effect by increasing general bodily requirements for protein It is also possible that certain poisons such as selenium and TNT can produce the condition by combining with components of protein so as to render them unusable

Studies on Hepatic Dysfunction Carbon Tetrachloride Poisoning Treated with Casein Digest and Methionine J Beattie P H Herbert C Wechtel and C W Steele report a case in which certain factors indicated a probable fatal outcome (1) large quantity of carbon tetrachloride ingested (2) probably complete absorption since immediate symptoms indicated a rapid entry into the circulation and vomiting was not induced until 45 minutes after ingestion (3) speed with which the liver enlarged and (4) delay between the accident and institution of treatment Miller and Whipple in 1942 showed that fatal liver damage was produced by 30 minutes of chloroform anesthesia administered to dogs which had been kept on protein deficient diets for sever

(4) B t M J 1 09211 F b 12 1944

damage was averted if within three to four hours after anesthesia 3 Gm methionine in solution was injected into the circulation Effect of carbon tetrachloride on the liver is comparable to that produced by chloroform

Soldier 23 ingested 30–40 ml carbon tetrachloride As he was physically fit and his diet was rich in protein it seemed possible that a massive dose of methionine intravenously might be effective despite the lap e of 19 hours since the accident A small oral dose (2 Gm) was administered pend ing preparation of a solution for intravenous infusion The infusion was prepared by dissolving 20 Gm of a dried papain trypsin digest of casein in 600 ml distilled water The solution was acidified and to it was added 15 Gm of dl methionine It was then boiled and filtered The final pH was 7 6 and the solution was approximately isotonic

The original intention was to administer 15 Gm methio nine calculated on the basis of 0 25 Gm per Kg body weight approximately the dose used by Miller and Whipple Only 9 5 Gm was infused because of a febrile reaction plus the 2 Gm given by mouth on the first day Casein digest was added because it was thought that amino acids other than methionine might be of value No methionine was given the following day A relapse on the third day treated by 4 Gm methionine orally suggested either that the first dose was too small or that small doses should have been admini tered on two or three days after the original massive dose It is also possible that had the infusion been slower reaction would have been averted and a larger dose might have been given originally as planned

The fourth day the patient was feeling well and wished to return to duty Abdominal palpation showed that the liver had retracted and was palpable about / in below the right costal margin on deep inspiration The liver edge was firm sharp and not tender The spleen could not be palpated The patient was kept under observation for another week during which he was symptom free and received no medica tion There was no evidence of icterus during the entire period of observation After two weeks on active duty on operational flights over enemy territory the patient was re examined he had no complaints had an excellent ap petite and said that he had been entirely fit since his dis charge Examination revealed no abnormal signs or symptoms

[The role of protein deficiency in the genesis of hepatic dis orders opens a new and illuminating chapter Of practical import appa ently is the u e of a casein ricl am no-acid methionine in the treatment of acute hepatic necrosis from whatever cause

toxic or nutritional Thus acute yellow atrophy and allied grave hepatic disorders promise to be less dreaded than heretofore judging from recent reports —Ed]

Experimental Hepatic Injury Paul Gyorgy (Univ of Pennsylvania) reports experiments on rats with use of diet forms in which the level of protein (casein) was lowered from 18 per cent in the original ration to 10 per cent or below Hepatic injury necrosis and/or cirrhosis became a regular occurrence to be produced at will in the course of a prolonged experimental period up to 150 days In the livers of rats in various groups receiving different percentages of casein and different supplements there is a great variety of pathologic change Fat infiltration in some degree is almost invariably present Parenchymatous or fatty degeneration with varying degrees of fat infiltration is less frequent There is no exact correlation between degree of fat infiltration and degree of necrosis or cirrhosis in the livers Most significant changes are diffuse or focal necrosis with or without accompanying hemorrhage and varying degrees of cirrhosis Necrosis is usually recognizable grossly but considerable cirrhosis may exist without being obvious macroscopically When cirrhosis is grossly visible the liver presents a rough nodular appearance (Fig 114) but not infrequently the surface is relatively smooth and gives no indication of degree of fibrosis

Application of results of experiments on rats *to conditions in man is allowable only within the limits of analogy* An unquestionable similarity of etiologic conditions prevails in cirrhosis in alcoholics and in these experiments Low intake of protein combined with insufficient supply of vitamin B complex (including choline) is a prominent feature of the daily diet of persons addicted to alcohol and is in good agreement with contributing conditions of dietary cirrhosis in rats It can be assumed that low intake of protein is in most if not all cases synonymous with insufficient supply of methionine Postulation of a specific injurious effect of alcohol becomes superfluous

(5) Am J Cl Path 14 (7 88 February 194

just as it does in pellagra or beriberi of alcoholism From the standpoint of general pathology it is interesting that identical etiologic conditions in rats may lead either to necrosis or to cirrhosis or both

The experiments reported were almost exclusively of a prophylactic nature However investigations are being extended to therapy of experimental cirrhosis and the impression has been gained that the same dietary factors



Fig 114 —C h t lj

which determine prevention of hepatic injury are equally effective when administered therapeutically In one rat (Fig 115) sudden appearance of ascites was followed by an almost equally rapid loss of weight after medication with cystine plus choline

These experimental data indicate that a similar attempt is warranted in reference to prevention and treatment of hepatic injury in man The following prophylactic and therapeutic dietaries present themselves (1) methionine in doses of 2–4 Gm daily or as a substitute but probably less effective cystine plus choline about 2–4

Gm each daily (2) use of a protein rich diet with high content of methionine as a substitute or further support for methionine and for cystine plus choline (3) limitation of fat intake and preferent use of fat rich in unsaturated fatty acids and low in cholesterol (4) inclusion of vitamin B complex with avoidance of an imbalance between members of the complex

These tentative recommendations refer to prevention

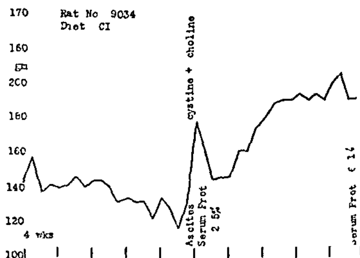


Fig 115—Weight curve of ... before and after treatment with cystine plus choline

and treatment not only of dietary hepatic injury but also of hepatic injury as it may follow toxic insults such as chloroform or other anesthesia exposure to TNT burns and surgical shock In acute cases transfusion with plasma enriched with methionine as a distinct therapeutic possibility Final test of the validity of these recommendations can be furnished by clinical observations alone

Effectiveness of Lipocaic in Preventing Fatty Livers in Completely Depancreatized Dogs Maintained with Insulin. C Entenman M Laurence Montgomery and I

L Chaikoff* (Univ of California) report results demonstrating that an amount of lipocaic prepared from 100 Gm pancreas does not maintain blood lipid values of depancreatized dogs at normal levels However 100 Gm raw pancreas contains more than enough of the blood lipid raising factor to prevent blood lipid values from falling below preoperative or normal levels Indeed previously it was found that as little as 5 5 Gm pancreas was sufficient to keep total fatty acid phospholipid and total lipid values at normal levels when fed as long as 20 weeks These results leave no doubt that lipocaic is a poor source of antifatty liver factor of the pancreas Six of nine dogs that received an amount equivalent to 100 Gm original pancreas 8–20 weeks had fatty livers

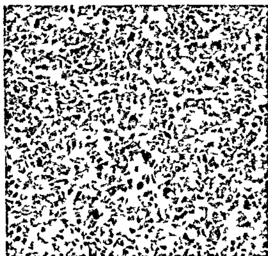


Fig 116—Ep d m b p t t Diff se acut b p tit l f l bul p tt n gul ty ll tain g w th l f glycog p ence f fl mm tory ll Best s carm sta d d f om × 160 (D bl s l b low)

Pathology of Acute Hepatitis Aspiration Biopsy Studies of Epidemic, Arsenotherapy and Serum Jaundice were made in 56 cases by J H Dible John McMichael

(*) Am J Phy l 141 2 1 6 Ap l 1944

and S P V Sherlock (London) Changes in the liver are related to severity and duration of the disease The picture is one of hepatic cell necrosis and autolysis associated with leukocytic and histiocytic reaction and infiltration The centers of the lobules show the first of these changes most markedly and the portal tracts the

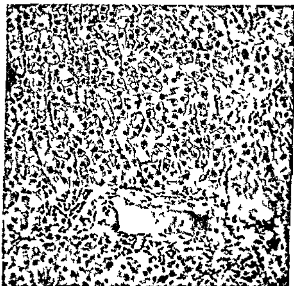


Fig 117—S m case as p ed ng one mo th l t Reco ery w th re ut t of lob l p tt a d d appea anc of fl mm to y lls So e n s d cll la ty em po t l t ct Hem toxyl n r du d f m × 160

greatest cellular infiltration In mild cases periportal cell accumulations predominate In more severe cases hepatic cell degeneration is more pronounced and histiocytic and leukocytic infiltration more widespread (Fig 116 and 117) For descriptive purposes the milder lesion is called zonal and the more severe diffuse An intermediate picture occurs which is designated mixed lesion Finally there are those cases in which the lesion is in the phase of retrogression or is progressing to a stage of necrosis nodular hyperplasia or cirrhosis

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Inflammatory lesions may be diffuse zonal or mixed Jaundice persisting over two weeks is more likely to be due to a zonal lesion Diffuse hepatitis usually heals completely and rapidly When the disease runs a longer course some residual fibrosis in the portal zones may be present after apparent clinical cure

No evidence was found that there is a form of jaundice caused by duodenal catarrh and obstruction of the common bile duct by mucus No histologic criteria were found for differentiation of lesions resulting from epidemic hepatitis arsenotherapy and serum inoculations

Acute Hepatitis in Soldiers after Inoculation with Yellow Fever Vaccine Especial Consideration of Severe Attacks Roy H Turner John Robert Snavely Edward B Grossman Robert N Buchanan and Stuart O Foster (M C A U S) report observation outlining the principal clinical features of postinoculation hepatitis as seen in a large epidemic among soldiers Severe attacks represented about 1 per cent of the epidemic cases The disease was indistinguishable clinically from conditions commonly known as infectious hepatitis or catarrhal jaundice The distinctive features were epidemiologic

Duration of disease weight loss and highest icterus index were criteria for an approximate classification These showed a high frequency of agreement only at extremes of severity Eighty one per cent of cases were classed as mild 17 per cent as moderately severe and 2 per cent as severe Detailed analysis of clinical features and results of laboratory studies permitted separation of severe cases into six groups In the first three of these the outcome was fatal (1) death appeared to be due solely to acute liver failure and brain dysfunction was the only evidence of extrahepatic injury (2) evidence of liver failure was extreme but in addition extrahepatic complications other than brain dysfunction appeared terminally (3) evidence of injury to extrahepatic organs was prominent The three groups classified as severe but not fatal included those in which (1) severity of the

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attack probably approached the maximum compatible with life with evidence of extrahepatic symptoms (2) severe attacks were differentiated from those in the preceding group by less frequent complications and better capacity to synthesize prothrombin and (3) attacks were classed as severe by duration and height of icterus index but the general picture of disease was otherwise mild The majority of severe cases were devoid of features indicating severity except prolonged marked icterus

Complications of hepatitis were dysfunction of central nervous system massive hemorrhages into the alimentary tract ascites sometimes with high protein concentration in the fluid renal dysfunction as manifested by albuminuria and isosthenuria skin rashes gingivitis hemorrhages into skin and mucous membranes Mental symptoms in the sickest patients resembled those seen in acute alcoholism hyperinsulinism and anoxia of the brain and indicated a grave prognosis Anemia next to petechial hemorrhages the commonest complication usually occurred late in the disease was commonly macrocytic and in a few instances developed rapidly and with manifestations indicating hemolysis Secondary injury of the liver and damage to extrahepatic tissues in complicated attacks may depend on failure consequent to injury and overloading of the system responsible for removal from the blood of products of lysis of hepatic cells and erythrocytes and of related substances

For estimation of degree of liver injury and as a basis of prognosis in severe attacks a valuable criterion was found in the number of days necessary for correction of prolonged prothrombin clotting after therapy with synthetic vitamin K was begun In general these clinical and laboratory observations are compatible with the concept that there are two kinds of pathologic processes in the liver one of which is sometimes predominant one causes injury or death to hepatic cord cells and the other obstruction to flow of bile and less commonly of blood the former is of brief duration and the latter

frequently dominates the picture throughout the illness

Warning is given of the danger of using liver function tests for diagnosis of surgically remediable biliary obstruction There was a tendency toward diminution in concentration of plasma albumin and increase of serum globulins without important change in concentration of total plasma proteins or of fibrinogen

Numerous observation indicated the great importance of rest in treatment and of regular frequent intake of food especially carbohydrate Quantitative estimations of appetite in a few patients indicated a preference for a diet of normal proportions Some failures in treatment are recorded

Structure of Liver after Recovery from Epidemic Hepatitis Few cases of epidemic hepatiti terminate in death most patients make a complete and apparently



Fig. 118 — … f m t al p t f l.b l n wh h to t is incompl t m ll g oup f l ll la k g S so d d t ded. S m d mato d thr gh t pa ly tter d lymphocyt d h t ocyt s. I tw h g t l m h se t f cul d l d w th b l

permanent clinical recovery To determine whether the liver is fully restored to normal condition or whether there is residual damage or progressive pathologic change Balduin Lucke (Army Med Museum Washington D C) studied liver structure in 14 patients who had re



Fig 119—I cent l p rt f lob l dest y d p nchym h not be n mpl t ly e t ed H p t c ds o g n m lly tow d l bul le At t m nal f th c d ell la g d h t y om t hyper hr m t l tl g t g ll a l ng th pty str m wh h con t a mod te n mt f lymphocyt d h t cyt Pe po tal t l ws m l ll and f w mall p l f t g b l d ct The is n e de f ew fo m t n of ll g u c n e t e d t e

covered from epidemic hepatitis 1 week to 14 months after the attack In 2 a fragment of liver was removed at abdominal operation 12 died of unrelated causes

Grossly all livers appeared entirely normal micro scopically the appearance varied somewhat with interval since recovery but in every instance integrity of all liver lobules was preserved In two patients who died of inter current disease during convalescence repair of liver lobule was still under way and cells lost from the central part

(9) Am J P th 0 595 619 May 1944

had not been entirely replaced (Figs 118 and 119) In three examined within a month after clinical recovery the liver lobules were entirely reconstituted but slight evidence of previou damage remained In nine others examined 1–14 months after recovery the liver parenchyma was restored completely (Figs 120 and 121) In less than half the cases traces of previous damage were found in the portal triads However the scarring was not found to be significant in any of these

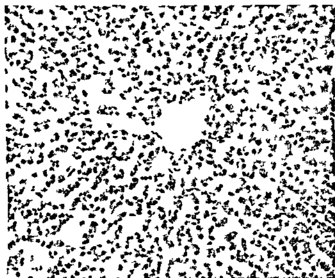
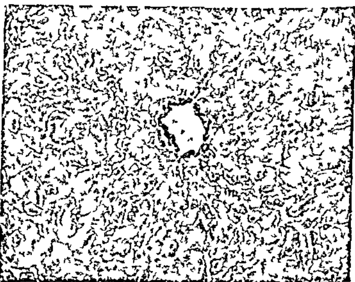


Fig 1 0—H r t 1 f 1 w th i f mal ppe g h p t ell g g tow d th w ll d t l t f p j y R tor t f ll g t k f p d m h p t t mpl te

Lucke conclude that complete restoration of hepatic parenchyma occurs in nonfatal cases of hepatitis coinciding with what is known about ability of the liver to regenerate Regeneration is usually complete provided destruction is acute and not continued and destructive changes involve only the hepatic cells not the framework or v l This is the case in epidemic hepatitis

[This and the preceding articles are additions to numerous recent similar contributions amplifying our knowledge of the morbid anatomy of acute epidemic hepatitis (catarrhal jaundice) as well as other forms of acute hepatitis —*Ed.*]

Cirrhosis of the Liver Clinical Aspects with Particular Reference to Liver Function Tests C J Watson[1] (Univ of Minnesota) states that diagnosis of cirrhosis may be



Fg 121—S me ca a p ec d g *R t c l m f* mew k t m l *pattern* of g ment ts m h enf ld n m l l cells. Walder s stain. (L ch p 673)

simple and obvious or quite difficult The history should include inquiry regarding previous jaundice *alcoholism* and dietary deficiency chemicals unexplained hematemesis and schistosomiasis On physical examination jaundice pigmentation hepatic facies and habitus spider nevi foetor hepaticus collateral circulation ascites and edema enlarged or small liver, enlarged spleen mental changes and coma should be kept in mind Laboratory tests should be made to determine *existence of jaundice of retention or regurgitation type* urobilinogenuria or variable disturbances of liver function Previous jaundice unrelated to *obvious biliary ob*

(1) Am. J Cl n P th 14 1 9 137 M h 19

struction and previous hepatitis are significant true catarrhal jaundice or mucous choledochitis probably has no etiologic importance Alcoholism is important in etiology of cirrhosis by producing fatty liver and because of associated chronic dietary deficiency but there is no reason to believe that moderate use of alcohol with adequate dietary protein produces cirrhosis Unexplained hematemesis always suggests cirrhosis and demands careful roentgen studies for esophageal varices and tests of liver function Jaundice small liver large multiple spider nevi and mental changes should direct attention to hepatic cirrhosis

The qualitative urobilinogen test especially if used serially and if strongly positive may be sufficient with history and physical findings to permit diagnosis of cirrhosis Relatively little urobilinogen may return to the liver in the portal circulation in the presence of (1) complete or high grade interference with outflow of bile (2) diminished formation of bilirubin because of reduced rate of blood destruction or throttling as in certain anemias (3) *diarrhea or other cause of malabsorption from* the colon or (4) renal insufficiency With any condition except the last the stercobilin tolerance test may be used in this a fixed load is given to the liver in a short time Under normal circumstances little or none of the injected stercobilin appears in *the urine* but considerable amounts appear quickly in bile in patients with liver damage large fractions or even the entire amount may be excreted in the urine The test is not used when native urobilinogen has already been found in amounts greater than 5 mg in 24 hours

Many have thought that presence or absence of urobilinogenuria was sufficient index of liver function others have advocated one or another liver function test as sufficient Increased study of liver function indicates that a single test is likely to be quite inadequate and in many cases numerous tests are necessary to provide a composite view or general index of liver function

Watson recommends a composite study determining hippuric acid in a one hour urine specimen after intra

[This and the preceding articles are additions to numerous recent similar contributions amplifying our knowledge of the morbid anatomy of acute epidemic hepatitis (catarrhal jaundice) as well as other forms of acute hepatitis —Ed.]

Cirrhosis of the Liver Clinical Aspects with Particular Reference to Liver Function Tests C J Watson (Univ of Minnesota) states that diagnosis of cirrhosis may be



Fig 121 —S m case p eced ng R t l m f w k ha n mal pattern of arra gen ent t mesh nf ld n mal l er cell Wilder s stain. (Lucke, p 673)

simple and obvious or quite difficult The history should include inquiry regarding previous jaundice alcoholism and dietary deficiency chemicals unexplained hematemesis and schistosomiasis On physical examination jaundice pigmentation hepatic facies and habitus spider nevi foetor hepaticus collateral circulation ascites and edema enlarged or small liver enlarged spleen mental changes and coma should be kept in mind Laboratory tests should be made to determine existence of jaundice of retention or regurgitation type urobilinogenuria or variable disturbances of liver function Previous jaundice unrelated to obvious biliary ob

(1) Am. J Cl n. Path. 14 129 137 M ch 19

ful are postnecrotic and congestive cirrhosis and that which occurs in schistosomiasis The syphilitic forms are not true cirrhosis There is no good reason for believing that a genuine tuberculous cirrhosis exists or that any other granulomatous disease produces true cirrhosis

Although the pathogenic process which leads to cirrhosis has many features common to the different forms and is essentially unitary there are varieties of cirrhosis which can be distinguished morphologically These anatomic forms are of such nature that certain items of etiology



Fig 12 (left) —L b P l f t f fib bl ts n po tal p d p t t t ghb g p t f l b l H mato yl n × 64
Fig 13 (right) —La ne b P l f t of fib bl t p t l l d p t t t ghbo g p t t l b l Mode t hlt ton by lymph yt d pl m ll H m to yl eo × 164

are implicated e g the cirrhosis due to extrahepatic biliary obstruction and tho e due to hemochromatosis xanthomatosis and Clonorchis sinensis If postnecrotic and congestive cirrhosis are included etiology is indicated in the names

[To those genuinely interested in the subject matter careful reading of th s exten ive review by an out tanding authority will be mply rewarded There till exists much difference of opinion among pathologists with re pect to essential deta ls —Ed]

Cardiac" or Congestive Cirrhosis Pathologic and Clinical Aspects are discussed by Simon Koletsky and James H Barnebee (Western Reserve Univ) Cardiac diseases studied included endocarditis lenta syphilitic

(3) Am. J M S 0 4 1 430 Ap 1 1944

venous injection of 1 77 Gm sodium benzoate serum albumin in Gm per cent serum globulin in Gm per cent cephalin cholesterol 0–4 plus bromsulfalein 2 mg per kg in per cent retained bromsulfalein 5 mg per kg in per cent retained total serum bilirubin in mg per cent urine urobilinogen in mg per 24 hours feces urobilinogen *in mg per 24 hours total serum cholesterol in mg per* cent prothrombin in per cent of normal bilirubin tolerance per cent retained 4 hours after 1 mg per kg intravenously stercobilin tolerance mg (as urobilinogen) appearing in 24 hour urine after 50 mg intravenously mg galactose in blood 75 minutes after 0 5 Gm per kg intravenously per cent response of prothrombin toward normal after 1 mg 2 methyl 1 4-naphthoquinone intravenously *serum phosphatase in units urine coproporphyrin in gamma* per 24 hours urine stool urobilinogen ratio

For mass screening as in chemical industries or the armed forces Watson recommends the following procedures (1) icterus index (fasting) (2) urine urobilinogen *(serial qualitative test) (3) cephalin-cholesterol* flocculation test of Hangar (4) bromsulfalein 2 mg per kg after 20 minutes Probably the second and third will yield the most information as to incipient liver damage

Watson suggests that pasteurized beef serum (which is now largely a discarded product) might have *possibilities* as a source of protein for patients with liver disease

Morphology and Pathogenesis of Hepatic Cirrhosis are discussed by Howard T Karsner[2] (Western Reserve Univ) Moon has incorporated the features of cirrhosis of the liver in a concise definition it is a *progressive* chronic diffuse inflammation accompanied by fibrosis retrogressive changes in the parenchymal cells and proliferation of remaining cells in the direction of regeneration This definition makes it possible to include as true cirrhosis the Laennec type (*Figs 122 and 123*) *fatty cirrhosis* hemochromatotic cirrhosis various forms of biliary cirrhosis including xanthomatous cirrhosis and the zooparasitic cirrhosis due to Clonorchis sinensis Somewhat doubt

(2) Am. J Clin Path 13 369 606 Nov 'ne 19

disease even though it is significant that a hereditary pre disposition to cirrhosis has been observed repeatedly since evidence is lacking to prove that it is present in all cases Shupbach reports two cases the first in which cirrhosis in father and son with telangiectasia was demonstrated histologically at autopsy In both cases there were acquired factors which were probably also involved in pathogenesis

Star nevi which may be multiple are frequently seen accompanying liver disease These are pinhead sized spots with slightly elevated red centers and starlike forma tions of tiny vessels radiating from them Central pulsa tion may be discerned by the palpating finger and often by visual examination with light pressure of a glass spatula These eruptions characteristically appear in the phase of exacerbation (liver insufficiency) and recede even to com plete disappearance with clinical improvement Hence they have both diagnostic and prognostic significance in liver disease Bouchard and Eppinger have described star nevi only with cirrhosis but they have also been observed in other hepatic diseases Schupbach reports two cases in women with severe hepatitis who exhibited this skin man ifestation Star nevi usually appear on the face neck shoulder anterior chest wall and back of the hands

The superficial similarity of star nevi and Osler s telan giectasias though the latter never pulsate and the rela tion of both to hepatic disturbances have caused such confusion that in many published reports the two condi tions are discussed together star nevi with liver disease may be spoken of as sporadic Osler s disease or a case of the familial disease of uncertain origin may be spoken of as recessive

In differential diagnosis Osler s disease can be distin guished by the hereditary factor and absence of central pulsation in the lesions of the skin and mucous mem branes in fact it is a true telangiectasia in the sense of capillary enlargement Disposition to bleeding especially nosebleed is *another indication of Osler s disease for it* is rare with star nevi The origin of the star nevi and their relation to liver disease are not clear and histologic

heart discase cor pulmonale coronary thrombosis hyper tensive heart disease *chronic constrictive pericarditis* and rheumatic heart disease divided as to forms into cases of aortic stenosis mitral stenosis and combined valvular lesions A group of 25 cases was selected for each type of cardiac disease except constrictive pericarditis in which only 8 were available these gave a total of 208 cases In every instance heart disease was the primary clinical lesion and the patient showed congestive failure After the number of cirrhotic livers in each type was determined a survey was made of 4 200 consecutive autopsies from which the various groups were drawn and the additional cases of cirrhosis were included in the study

Livers that are the seat of prolonged and advanced passive hyperemia caused by heart failure sometimes show diffuse fibrosis and alteration of architectural pattern These may properly be designated congestive cirrhosis However degree of fibrosis and distortion of architectural pattern are considerably less than in well developed Laennec s cirrhosis The main etiologic factor is prolonged and severe hepatic venous stasis Repeated episodes of decompensation favor development of the lesion

The most severe degree of fibrosis and architectural change occurred in patients with chronic constrictive pericarditis Continual venous stasis in such cases suggests that cirrhosis develops as a progressive process Congestive cirrhosis is relatively common in patients with rheumatic heart disease in those with mitral stenosis or with combined valvular lesions It is less frequent in hypertensive patients and is uncommon or rare in those with other etiologic forms of heart disease Clinical aspects of congestive cirrhosis do not provide adequate data for antemortem diagnosis

Telangiectatic Manifestations and Liver Disease are discussed by A Shupbach with special reference to Osler s disease and liver cirrhosis and eruptive pulsating star nevi with liver disease He emphasizes that cirrhosis cannot be regarded as a constant factor in familial Osler s

(4) S hw med. W hnsch 73 1186 1189 S 1

disease and suggest that further exploration of the factors concerned is necessary before it can be clarified

New Aid in Control of Hemorrhage in Severe Damage to the Liver *Transfusions of Blood Fortified* **by Administration of Vitamin K to Donors** Roy E Kinsey reports 5 cases of acute yellow atrophy among 663 of intrahepatic jaundice observed at Camp Blanding Fla Plasma prothrombin was reduced to such an extent that severe *spontaneous hemorrhages* occurred The patients received large doses of vitamin K without benefit and large transfusions of whole blood with minimal changes in prothrombin and no effect on bleeding The first patient was given 10–30 mg menadione intramuscularly and 1 000–2 000 cc whole blood daily Despite this prothrombin fell to 8 per cent of normal bleeding increased and the patient died *of generalized hemorrhages and hepatic failure* Autopsy revealed a small liver with severe yellow atrophy and large generalized hemorrhages

In view of this failure and similar observations by others that severely damaged livers do not respond to vitamin K it was decided to try transfusions of blood fortified by administration of vitamin K to donors This *method* was *suggested by the obstetrician s administration* of vitamin K to the mother prior to delivery even though her prothrombin level is normal to prevent deficiency of prothrombin in the new born infant

This procedure produced remarkable effect in controlling bleeding tendencies in all four patients although three succumbed to the liver disease Maximal elevation of *prothrombin usually occurred within 24 hours after trans*fusion but in cases in which the liver was still badly damaged there was usually a decline during the second 24 hours A striking feature in one case was the regularity with which bleeding ceased 120–140 minutes after transfusion on all occasions In two cases fortified transfusions as well as regular transfusions had no effect on a minute purpuric *rash but controlled hemorrhages in skin* and subcutaneous tissues

(6) A k I M d 3 131 137 F b 1944

study has been inadequate It is essential for clarification in future studies that observers differentiate the Osler manifestations from star nevi in hepatic disturbances

[Telangiectasias star nevi or pulsating telangiomas can be easily overlooked during the physical examination Such lesions like an enlarged spleen are extremely helpful in establishing or confirming a diagnosis of hepatic cirrhosis —Ed]

Association of Cirrhosis, Thrombopenia and Hemorrhagic Tendency Carl G Morlock and Byron E Hall (Mayo Clinic) call attention to the possibility that factors other than the concentration of prothrombin may be of significance in explaining the aberrations from normal noted in the mechanism of coagulation of blood in cases of severe damage to the liver Their attention was recently turned to the possibility that thrombopenia might be an important factor in explaining the severe hemorrhagic tendency sometimes encountered in hepatic disease A series of 80 cases of hepatic cirrhosis was reviewed and definite thrombopenia was found in 17 5 per cent Although a definite hemorrhagic tendency was evident in many of these cases regardless of blood platelet level it was relatively twice as frequent when thrombopenia was associated However a hemorrhagic tendency is not exhibited in all cases of thrombopenia for in 2 of 14 cases of cirrhosis and thrombopenia no bleeding of any kind occurred

The records of 50 cases of splenic anemia were also studied Incidence of thrombopenia was higher than in the cases of cirrhosis and incidence of bleeding was increased correspondingly The tendency to bleed was greater with a significant reduction in the level of thrombocytes

The authors believe that the diminution of blood platelets in severe hepatic disease of long standing is not a chance and unimportant finding In their study they did not discover an explanation for this alteration but they feel that in its presence the bleeding hazard is definitely increased Their observations serve to emphasize the complexity of the important problem of bleeding in hepatic

(5) Arch Int Med. 72 69 77, July 1943

Amebic Abscess of Liver Unsuspected until Perforation. Waltman Walters Charles H Watkins Hugh R Butt and James M Marshall (M C U S N R) report two cases in which symptoms occurred only when the abscess perforated to the right subdiaphragmatic region Both patients had had naval duty at one or more of the South Pacific islands and had been returned to the main land with a diagnosis of lymphadenitis In neither case was diarrhea present nor were amebas found in the stools In Case 1 the general condition improved after administration of emetine (Fig 124) but the subdiaphragmatic abscess increased in size and open operation was performed In Case 2 there was no apparent response to emetine Because of the patient s critical condition surgical drainage was performed as an emergency procedure Both patients made excellent recoveries

Primary Carcinoma of Liver Dwight L Wilbur David A Wood and Forrest M Willett (Stanford Univ) report a study of 49 cases Adequate clinical data were available in 40 and pathologic data in all Forty seven patients were males Occurrence of nine cases in Chinese (19 per cent) is striking in view of the relatively low percentage of Chinese in the total population Nine patients were aged 40 or less In one of these the neoplasm was probably prenatal as an abdominal mass was discovered three days after birth The infant died of primary carcinoma of the liver at 3 months

The two classic types of primary epithelial liver tumors were observed 45 cases were liver cell carcinomas (Figs 125 and 126) and only 4 originated in epithelium of intrahepatic bile ducts The most commonly observed clinical symptoms were an abdominal mass abdominal pain jaundice ascites weight loss and edema of the legs These symptoms are nonspecific in the sense that no grouping of them is characteristic or diagnostic of the disease Clinical and pathologic data could not be satisfactorily corre

(7) J A M A 125 963 966 Aug 5 1944
(8) Ann. Int. Med. 20 453 485 Mar 1944

Determination of the optimal amount of vitamin K and time required for its utilization by the donor requires further study but 6–10 mg menadione given intramuscularly during the 24 hours before transfusion will work satisfactorily

Kinsey comments that the few cases variations in preparation of donors and the necessity of using two different technics in prothrombin determinations prevent specific conclusions but the evidence indicates that this method may have definite value in preventing immediate hemorrhagic death in acute yellow atrophy or in controlling hemorrhage until there has been regeneration of sufficient hepatic tissue for essential functions

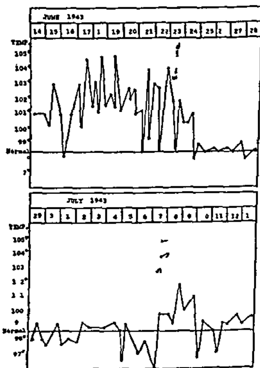


Fig 124—Temperature chart showing intermittent fever of ... pattern of amebic abscess of liver to right subphrenic ... response to full course of emetine therapy (White ... (85))

lated to establish clinical criteria for diagnosis of any particular type of primary carcinoma of the liver

Gross bleeding into the peritoneal cavity occurred in 12 patients and was a significant factor in causing death In one case in a youth 19 marked clinical hypothermia was striking although it cannot be stated definitely that it was the result of primary liver carcinoma.

Cirrhosis as a coexistent lesion was found in 27 cases Three of these were cases of hemochromatosis Although incidence of portal cirrhosis has doubled in the last 7½ years the percentage of cases of cirrhosis associated with primary carcinoma of the liver has decreased slightly In 56 cases the liver was increased in size Peritoneal fluid was noted in 44 in 28 it exceeded 1 000 cc Many of the tumors were anaplastic However bile formation was demonstrated in 17 Incidence of extrahepatic metastases is low Organs other than the liver were involved only 26 times in contrast to 44 cases with intrahepatic metastases

Syphilis of the Liver Richard D Hahn (Johns Hopkins Univ) attempts to delineate clearly the pathologic anatomy and clinical picture of true syphilis of the liver The nature of the few available pathologic observations lends credence to the theory that an actual diffuse syphilitic hepatitis is the basis of the jaundice seen in association with untreated secondary syphilis Diagnostic criteria include the coexistence of jaundice with infectious lesions a benign course and rapid response to antisyphilitic treatment Early syphilis of the liver has not been observed at autopsy at Johns Hopkins Hospital and clinical diagnosis has been made in only 5 of approximately 10 000 patients with early syphilis

No support is afforded the concepts that early post arsphenamine jaundice is a Herxheimer effect or that delayed postarsphenamine jaundice is a hepatic mono recidive Diagnostic criteria of a true hepatorecurrence include the appearance of jaundice in association with mucocutaneous relapse and its prompt disappearance on

(9) Am J Syph. Go & V n D 27 5 9 56 September 1943

F 1 5 —Mod t ly nl g l d ff ely od la l e f om po t rior a j t f g l cap l t m f tly d ce bl t d me f right l be t f t m t f p t Nod l h l l d ppear c du to b th c hos s and t m



Fg 1 6—T s se t f l w gh ng 80 Cm Primary t mor in l tt l be

even usual manifestation Abdominal pain occurring in 12 patients was the most significant subjective complaint its sole distinguishing characteristic was prompt response to antisyphilitic treatment Less frequent complaints were history of weight loss abdominal swelling severe gastro intestinal symptoms febrile episodes jaundice or bleeding The most frequent physical finding was a palpable liver noted in 23 patients enlargement to more than 3 cm below the costal margin coarse nodularity tenderness and predominantly unilobar enlargement were present in 10 9 7 and 5 respectively In 10 patients the spleen was palpable jaundice and ascites in the absence of contributory factors were noted in 9 and 8 patients respectively Gross gastro intestinal hemorrhage occurred only twice Significant temperature elevation usually not marked was present 12 times Sixty six per cent of the 73 patients presented other evidences of syphilis on physical examination Serologic test for syphilis was positive in 81 per cent of 63 patients Anemia and leukocytosis were rare No patient with late syphilis of the liver had received adequate therapy for early syphilis The median estimated duration of syphilis at the time of death or laparotomy was 15 years

It is estimated that in only 6 of every 1 000 syphilitics is late hepatic syphilis a contributory cause of death Additional evidences of its benign nature were absence of significant clinical manifestations in 70 per cent of the 75 patients and the prolonged course of the disease in the *remaining 30 per cent The correct diagnosis had been* suggested in only 12 3 per cent of the total and in 19 per cent of the latter group Portal cirrhosis and carcinoma of the liver accounted for over 50 per cent of the erroneous diagnoses recorded for those patients presenting clinical evidence of hepatic disease

Erroneous diagnosis was shown not only by failure to recognize the presence of hepatic syphilis but also by the diagnosis of other conditions as hepatic syphilis The clinical diagnosis proved correct in *only 9 of 35* patients with an original diagnosis of syphilis of the liver

resumption of antisyphilitic treatment In the author s material only one case conformed to these criteria

Acute yellow atrophy of the liver in association with untreated early syphilis was not observed clinically or at autopsy The almost complete absence of authenticated cases in modern literature the nonspecificity of the pathologic changes the consistent failure to demonstrate the causative organism and the definite relationship to arsenical therapy cast doubt on the existence of such an entity as icterus syphiliticus gravis

The gross autopsy incidence of late syphilis of the liver was 0 45 per cent incidence at autopsy among 1 165 syphilitics was 4 9 per cent A study by race sex and age revealed no significant differences

Analysis of the anatomic findings at autopsy in 66 cases of late hepatic syphilis failed to reveal a specific syphilitic diffuse interstitial hepatitis The most outstanding characteristic was the focal gummous nature of the process Large irregular surface scars which descended into the parenchyma branching out in a stellate manner were the most frequent anatomic findings These scars originated in the healing of gummas which were located almost exclusively within them With this healing contraction occurred with distortion of liver tissue resulting ultimately if the process was sufficiently extensive in typical hepar lobatum Not infrequently the process was confined predominantly to one lobe There was no generalized destruction of the architectural pattern of the anatomic lobule The essentially benign nature of the lesion accounted for the frequency with which the healed stage was present In only eight cases had the pathologic process in the liver been an apparent contributory cause of death Average weights of both liver and spleen were below adult normal only 3 of 61 livers weighed more than 2 200 Gm and only 8 of 59 spleens weighed more than 300 Gm Of the 66 patients 40 presented anatomic evidence of syphilis in other organs

An analysis of clinical findings in 73 verified cases of late syphilis of the liver revealed no sin[illegible] nt or

with which portal cirrho is occurred in association with definite hepatic syphilis and the absence of transition forms between the two types of pathologic processes as well as the identity of portal cirrhosis in syphilitic and non syphilitic patients with respect to pathologic anatomy incidence by race and sex and temporal distribution of ca es by four year periods

[This is an important contribution to our knowledge of the subject and is based on factual data The author's observations are at variance with those of some well known syphilologists and clinicians These ob ervation also help to clarify the problem of diagnosis and therapy in tho e confusing instances when a syphilitic happens to have atrophic cirrho i —Ed]

Peritoneoscopy in Liver Disease Edward B Benedict (Harvard Univ) reports that of 435 cases in which peritoneoscopy was performed the question of liver disease arose in 331 (70 per cent) Liver disease was found in 260 cases (see Table) In the remaining 71 an essentially normal liver was revealed

Peritoneoscopy is an important and well established

CLASSIFICATION OF CA ES OF LIVER DISEASE

Mal g		No mal nt	
Metastatic carcinoma	170	Cirrhosis	73
Primary carcinoma	5	Cholangit s	2
Melanotic sarcoma	1	Banti s disease	2
M lignant lymphom	1	Lymphangioma	2
		Polycystic liver	1
T tal	177	Echinococcus cyst	1
		Sarcoid	1
		Enlarged liver	1
		Total	83

method of examining the peritoneal cavity and is especially applicable to differential diagnosis of liver disease for with biopsy a suspected diagnosis is made positive Since many patients are seriously ill and in most of them an exploratory laparotomy is contraindicated value of precise diagnosis by peritoneoscopy is apparent It requires only a 1 cm incision under local anesthesia an overnight stay in the hospital and minimal risk or discomfort to the patient

(1) New E gl d J M d 30 1 5 130 F b 3 1944

seen ultimately at autopsy or laparotomy over 40 per cent had portal cirrhosis and almost 20 per cent had carcinoma of the liver

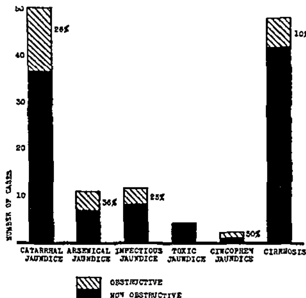
The diagnosis of other conditions as hepatic syphilis may be expected to become less frequent with realization that late yphilis of the liver rarely produces arresting symptoms with abandonment of the nebulous concept of syphilitic cirrhosis and of the fallacious use of a palpable liver as the sole criterion for diagnosis and with proper interpretation of the therapeutic test In particular hepatic syphilis rarely produces ascites huge liver pronounced evidence of weight loss high septic fever or severe toxemia If however in associaiton with a large coarsely nodular liver the spleen is palpable the diagnosis of hepatic syphilis is more tenable The therapeutic test may be adjudged definitely positive only if there is a striking change in objective manifestations in direct tem poral relationship to antisyphilitic treatment and if such change is maintained over a long observation period Only by such prolonged observation can spontaneous change in conditions of other etiology be eliminated In the presence of an active process in the liver manifested by fever and local pain or tenderness a rapid presumptive therapeutic test is feasible In the absence of signs of *activity the* therapeutic test has only limited value

There was no evidence that hepatic damage due *to* syphilis predisposed to hepatic damage by arsenicals The therapeutic paradox was not observed Nevertheless be cause of the possibility of lesions at the hilus treatment should be initiated with bismuth and iodides In the presence of ascites arsenotherapy would appear to be contraindicated

Portal cirrhosi was *found at autopsy in 3 8 per cent* of 1 165 adult syphilitics and in 2 3 per cent of 4 505 adult nonsyphilitics Significant difference in incidence *disappeared on* elimination of *cases* of cirrhosis which occurred in adequately treated syphilitics Other cogent reasons against the assumption of an etiologic relationship *between syphilis* and portal cirrhosis inclu rarity

hepatitis but only two such cases were observed But even in catarrhal jaundice or infectious hepatitis the incidence is significant being 26 and 25 per cent respectively

In most cases intrahepatic obstruction lasted only a few days but in some it persisted for almost a month Duration of obstruction was unrelated to the causal mechanism



I g 127 —I de f b t ct ph omeno case f cut h p t ti ord g t t l g g p g d n h w th j d ce

In general patients with obstruction are more acutely ill and present more severe impairment of liver function than do patients without obstruction and the icterus index is usually higher As would be expected urobilinogen levels are lower in the presence of obstruction However in obstruction the other liver functions unrelated to bilirubin excretion are also relatively more impaired as indicated especially by the relative reduction of cholesterol esters and hippuric acid excretion The difference in serum

Preparation of the patient with liver disease for peritoneoscopy is important for frequently there are jaundice and liver damage If prothrombin time is prolonged vitamin K is administered to reduce bleeding Morphine and its derivatives and barbiturates are to be avoided Chloral hydrate may be safely substituted Otherwise the patient is prepared as for any laparotomy including an abdominal shave and scrub and emptying of stomach and bladder The usual site of puncture for inspection of the liver is in the midline just above the umbilicus

[Our own experience is in conformity with that of Benedict. It is a trustworthy safe and expeditious diagnostic procedure in experienced hands as a rule—Ed]

Intrahepatic Obstructive Jaundice Absence of bile from the duodenal contents and stool and of urobilinogen from the urine of a jaundiced patient indicates biliary obstruction usually requiring surgical intervention Diagnosis is more probable if these findings appear on repeated examinations However this phenomenon does not always indicate jaundice of a surgical nature for it may also be associated with well established hepatitis[2] thus confusing the differential diagnosis of surgical and medical jaundice To elucidate such situations Frederick Steigmann and Hans Popper (Univ of Illinois) discuss the incidence and significance of medical jaundice

Among 563 cases of jaundice of all types were 127 due to hepatitis in which the etiologic factors could be ascertained with fair accuracy and of these 26 showed the obstructive phenomenon The 127 included 48 cases of cirrhosis with jaundice due to acute hepatitis and 5 of these presented obstruction In 21 of the remaining 79 cases of acute hepatitis of variable etiology temporary intrahepatic obstruction occurred

Study of the 79 cases of acute hepatitis in an attempt to correlate etiologic factors with obstruction (Fig 127) disclosed the relative incidence of the obstructive phenomenon to be highest in cases of arsphenamine hepatitis (36 per cent) A high incidence was also noted in cinchophen

(2) Ca t oenter logy 1 645 654 July 1943

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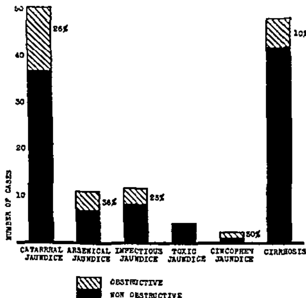


Fig 127 —I ciden e f b tr cti ph nomen n case f t h p t t accord g t t l g group g d h w th j d ce

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phosphatase levels is not significant average being 19 units in the obstructive group and 17 units in the non obstructive group Results of galactose tests only are at variance with these general findings in that fewer patients with obstruction manifest a positive galactose tolerance test

The mechanism of this phenomenon seems to be a toxic exudative reaction affecting the periportal field with compression of the junction between the bile capillaries and bile ducts or of the canal of Hering

Carcinoma of the Gallbladder Clinical and Pathologic Study is reported by James I Vadheim Howard K Gray and Malcolm B Dockerty[3] (Mayo Clinic) Clinical records surgical end results and results of gross and microscopic study of pathologic specimens were reviewed and correlated in 77 cases

Carcinoma of the gallbladder occurs most frequently in the fifth decade and is predominantly a disease of women Stones were associated with the carcinoma in 88 per cent of cases and there was evidence that they definitely preceded development of carcinoma in 58 5 per cent Analysis of early symptoms revealed nothing which could not be attributed to presence of chronic inflammation of the gallbladder with or without cholelithiasis

Classification of these carcinomas revealed adenocarcinoma 85 3 per cent squamous cell carcinoma 2 7 per cent adeno-acanthoma 12 per cent. Three instances of malignant degeneration in a papilloma and one in an adenoma were found Finding of areas of metaplasia in the mucosa and of adenocarcinoma and squamous cell carcinoma in the same tumor lends support to the theory that metaplasia is responsible for the origin of a squamous cell carcinoma

Five year cures were obtained in 45 per cent of cases of carcinoma grade 1 in 4 3 per cent in cases of grade 2 and in none of the cases of carcinoma of the other grades In no instance was a definite diagnosis made preoperatively

(3) Am. J Surg 63 173 180 February 1944

Quantitative Urobilinogen Determinations in Differential Diagnosis of Jaundice *According to Frederick Steigmann and Josephine M Dyniewicz* (Univ of Illinois) differentiation of the several types of jaundice is aided by repeated quantitative determinations of urobilinogen in the urine and stools Such determinations were performed in 259 cases of jaundice and compared with results of various liver function tests clinical course and findings at operation or autopsy Normal values are presented in Figure 128

Fig 128—F ly on ta t b l g d fl t ting tool b l no g n (w th n norm l ges) n normal pe son.

(4) G t oe te l gy 1 855 8 5 S pt be 194

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Carcinoma of the Gallbladder Clinical and Pathologic Study *is reported by* James I Vadheim Howard K Gray and Malcolm B Dockerty (Mayo Clinic) Clinical records surgical end results and results of gross and microscopic study of pathologic specimens were reviewed and correlated in 77 cases

Carcinoma of the gallbladder occurs most frequently in the fifth decade and is predominantly a disease of women Stones were associated with the carcinoma in 88 per cent *of cases* and there was evidence *that they definitely pre*ceded development of carcinoma in 58 5 per cent Analysis of early symptoms revealed nothing which could not be attributed *to presence of chronic inflammation* of the gallbladder with or without cholelithiasis

Classification of these carcinomas revealed adenocarcinoma 85 3 per cent squamous cell carcinoma 2 7 per cent adeno acanthoma 12 per cent Three instances of *malignant degeneration in a papilloma and one in an* adenoma were found Finding of areas of metaplasia in the mucosa and of adenocarcinoma and squamous cell carcinoma in the same tumor lends support to the theory that metaplasia is responsible for the origin of a squamous cell carcinoma

Five year cures were obtained in 45 per cent of cases of carcinoma grade 1 in 4 3 per cent in cases of grade 2 and *in none of the cases of carcinoma of the* other grades In no instance was a definite diagnosis made preoperatively

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(3) Am. J S g 63 173 180 F b uary 1944

Quantitative Urobilinogen Determinations in Differential Diagnosis of Jaundice According to Frederick Steigmann and Josephine M Dyniewicz (Univ of Illinois) differentiation of the several types of jaundice is aided by repeated quantitative determinations of urobilino

Fig 128 —F ly con t t n l l g d fi t ti g tool rb l g (w th n mal ge) n normal pe son

gen in the urine and stools Such determinations were performed in 259 cases of jaundice and compared with results of various liver function tests clinical course and findings at operation or autopsy Normal values are presented in Figure 128

(4) C t oe t l gy 1 855 8 5 S pt be 194

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Patients with icterus due to cholelithiasis show only a slight increase in the amount of urobilinogen in the urine except with complicating factors such as acute cholangitis or biliary cirrhosis The rise in urobilinogen caused by

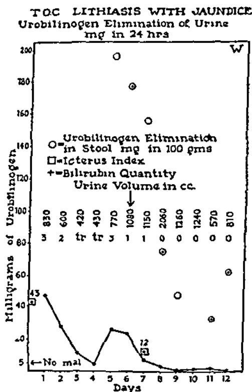


Fig. 1 9—Comparat ly h gh b l og n al n r and tool with fl t t s cholel th a s

such complications is dependent on the degree of associated biliary obstruction and the consequent amount of urobilinogen formed and reabsorbed from the bowel Jaundice due to stone is rarely accompanied by complete biliary obstruction so that persistent values of less than 5 mg fecal urobilinogen per day or traces of urobilinogen in the urine are rare in jaundice due to cholelithic obstruction

Urobilinogen values in the stool may fluctuate (Fig 129)

Obstruction due to malignancy is almost always complete so that the amount of fecal urobilinogen is less than 5 mg per day and the urine shows no urobilinogen or mere traces An exception to this may be found in cases

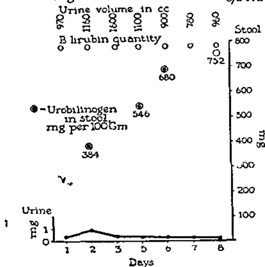


Fig 130 — U ry b l g m l b t fecal b l n g h gh h m l t j d

of jaundice due to carcinoma of the ampulla of Vater in which intermittent urobilinogenuria occurs

Icterus due to hepatitis is usually associated with marked urobilinogenuria This increase varies depending on the degree of hepatic damage although the urobilinogen is not always elevated in the presence of other signs of liver disease In some instances of severe toxic hepatitis particularly in those due to arsenical intoxication and in cases of obstructive cirrhosis the urobilinogen in both urine and feces may temporarily reach very low level

simulating but not actually imitating complete obstruction due to neoplasm In simple hepatitis the fecal urobilinogen values are usually low except when an additional component of blood destruction is present In the latter the amount of urobilinogen in the feces is also increased

In hemolytic jaundice the amount of urobilinogen in the urine is only slightly increased but the fecal urobilinogen attains high values (Fig 130) With improvement the fecal urobilinogen drops to high normal values Associated hepatic dysfunction has been noted in some patients of this group as disclosed by other liver function tests

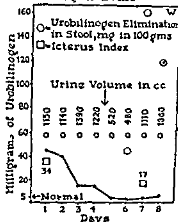


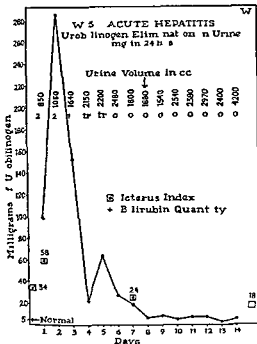
Fig 131—High urinary urobilinogen in hepatitis at height of disease with improvement urinary urobilinogen and icterus index drop and fecal urobilinogen rises

[This is one of the first investigations of its kind on a large scale exclusive of those carried out by Cecil Watson Watson has pioneered in this field not only from the standpoint of laboratory technic but from the clinical view that is the application of the results of quantitative urobilin excretion tests to differential diagnosis of conditions associated with jaundice The results of this study are in large measure in conformity with those of Watson and are added testimony to the diagnostic efficacy of the procedure in doubtful cases —Ed]

Methods of Diagnosis of Jaundice In a previous study Franklin W White reported errors in diagnosis in 500 cases of jaundice observed at Boston City Hospital He now reviews clinical and laboratory methods that proved most useful in diagnosis of these cases including complete and partial biliary obstruction acute and subacute

(5) New England J M 1 30 344 348 Mar 3 1944

infectious and toxic hepatitis the cirrhoses (portal biliary pigmentary toxic and cardiac) fatty liver tumors and syphilis of the liver and hemolytic anemia Because of variation of symptoms latent or exceptional cases multiple diseases in a single patient and multiple factors comprising the clinical picture the number of possible com



F g 132—Rec f u y b l g p t t w th h p t t f two d y ft adm nd d p th mp m t (St gm Dy w p 695)

binations of symptoms and signs in any given disease causing jaundice is large and 100 per cent diagnostic accuracy can never be attained Diagnosis may be laboriously built up from a collection of clues or may be obvious at once as in arsphenamine hepatitis prolonged painless

complete obstruction and chronic low grade familial hemolytic anemia Age incidence in four important groups is shown in Table 1 Painless jaundice in youth first suggests infectious hepatitis and in patients over 50 cholecystitis cirrhosis or tumor

TABLE 1—AGE INCIDENCE

Diagnosis	Cases	Percentages Under 30	30–50	Over 50
Acute infectious hepatitis	101[1]	40	32	27
Cholecystitis	71	15	31	53
Cirrhosis	161	9	40	51
Tumors of liver and bile passages	83	0	19	81

The course of the jaundice often aids diagnosis and since cases of jaundice are rarely emergencies a short study period is useful Tests of liver function should be repeated in series A short course of moderate to severe jaundice with marked loss of liver function was due oftener to *hepatocellular damage than to obstruction Acute deep* jaundice with brown stools was almost always of hepatocellular type

Value of depth of jaundice liver size and a palpable gallbladder was often overestimated in differential diagnosis The icteric indexes in acute hepatitis and complete external biliary obstruction were much alike (Table 2)

TABLE 2—MAXIMUM RANGE AND AVERAGES OF ICTERIC INDEX

Diagnosis	Cases	Range of Max.	Av. Max.
Acute hepatitis			
Infectious	17	22–250	102
Toxic	17	50–200	115
Complete obstruction	31	65–200	116
Cirrhosis and partial obstruction	35	10–225	59
Total	100		

An enlarged liver was a valuable sign of hepatic disease but was so common that it gave little help in deciding the kind The gallbladder could be palpated in only one third of the cases of malignant obstruction of the common duct complete absence of bile from the stools was more frequent and constituted important evidence of obstructive tumor Complete obstruction due to cancer almost never improved

The spleen was not palpable in any case with tumor

ot the liver but was felt in 27 per cent of cirrhotic cases Spider angiomas were found only in portal cirrhosis Fever and leukocytosis in late cancer sometimes simulated cholangitis and liver abscess In deep jaundice an absence of bilirubin in the urine suggested hemolytic anemia a diagnosis readily confirmed by other tests

The test for urobilinogen in the urine often furnished *direct aid in diagnosis of complete obstruction from* hepatocellular damage and from partial obstruction Reactions to other tests such as hippuric acid and bromsulfalein excretion were positive in all types of liver disease *and had no differential value Some tests useful in prognosis* and for which differential value has also been claimed such as amount of cholesterol ester in the blood prothrombin level and its response to vitamin K and changes in levels of serum proteins and in albumin globulin ratio had little or no differential value In diagnosis of acute pancreatitis with jaundice early tests for diastase in the urine proved simple and valuable Positive Hinton Kahn or Wassermann reactions in jaundiced patients usually did not indicate syphilis of the liver Roentgen studies often detected gallbladder disease the primary source of a cancer of the liver and esophageal varices During deep jaundice the Graham test had little value because of poor excretion of dye by the liver

Clinical Evaluation of Some Tests of Liver Function. C Higgins J R P O'Brien Alice Stewart and L J Witts estimated bilirubin phosphatase albumin and globulin levels in the plasma and measured hippuric acid excretion and levulose tolerance in 100 healthy students and laboratory workers 71 patients with liver disease and 62 with other diseases

A combination of data from the same individual yields more diagnostic information than can be obtained from any single test The level of plasma phosphatase is proportional to that of bilirubin in jaundice due to biliary obstruction whereas abnormalities of plasma phosphatase levulose tolerance or hippuric acid excretion do not occur

in jaundice due solely to hemolysis Nonjaundiced patients with cirrhosis who have ascites or unusual nutritional disturbances show disturbance in plasma proteins and faulty levulose tolerance whereas patients with myelomatosis who have an abnormal albumin globulin ratio have none of the other changes in blood chemistry found in liver disease In subacute hepatitis a moderate rise in bilirubin and phosphatase is accompanied by striking changes in plasma proteins and a gross reduction in levulose tolerance In carcinoma with extrahepatic obstruction jaundice is associated with a rise in phosphatase there usually is no change in plasma globulin and levulose tolerance is not greatly impaired Changes in carcinoma of the liver without extrahepatic obstruction are the same except that jaundice is not intense the phosphatase level is still notably raised

The tests are not equally useful in different stages of hepatitis Plasma bilirubin level is a reliable guide to immediate prognosis in acute hepatitis but of little value in subacute and chronic forms Plasma phosphatase determination and the hippuric acid test often give valuable supporting evidence of liver damage but are not reliable enough to be used as individual tests for diagnosis or prognosis Levulose index may be unobtainable in acute hepatitis and it adds nothing to clinical knowledge of this stage In subacute and chronic hepatitis it is a good index of the degree of liver damage It is inconvenient in clinical practice as it involves repeated venipuncture

Disturbances of plasma proteins are relatively slight in acute hepatitis but are the outstanding feature in subacute and chronic cases Normal values are fairly rapidly restored if the patient recovers completely but a persistent alteration of albumin globulin ratio indicates that the liver has suffered irreparable damage In chronic hepatitis adequate liver function may be maintained if there is more than 3 5 Gm per cent albumin but below this the margin of reserve is poor A fall below 2 Gm per cent albumin is of grave significance In subacute hepatitis with progressive liver disease an improve[illegible] [illegible]

albumin level coincides with clinical remissions A rise in plasma globulin is common in all varieties of hepatitis A close correlation exists between changes in plasma proteins prognosis and duration of jaundice

Estimation of bilirubin phosphatase albumin and globulin in the plasma from a single blood specimen usually provides as much diagnostic and prognostic information as can be obtained from more elaborate tests of liver function such as levulose tolerance and hippuric acid excretion

***Clinical Value of Liver Function Tests with Particular* Reference to Hippuric Acid Test** is discussed by Armand J Quick (Marquette Univ) The oral hippuric acid test is simple cheap and safe the main difficulty encountered is vomiting and theoretically delayed absorption of sodium benzoate may lead to erroneous results The intravenous modification consisting in injecting 1 77 Gm sodium benzoate dissolved in 200 cc water successfully precludes these disadvantage Urine is collected one hour after injection and hippuric acid determined A normal adult will excrete 1–1 4 Gm hippuric acid (0 68–0 9 benzoic acid) This method is a little more difficult than the oral test since care must be taken in injecting the solution if it is given too fast transient but rather severe pain may occur along the vein It is also somewhat more expensive since it is advisable to use commercially prepared ampules

Both oral and intravenous hippuric acid tests are established by numerous clinical studies as reliable methods for estimating liver dysfunction and damage Factors interfering with accuracy are inanition dehydration and poor kidney function Excretion of hippuric acid tends to be decreased at the end of pregnancy and at the beginning of menstruation causes of hyperexcretion are not known and its clinical significance has not been determined

Prothrombin test in response to vitamin K is useful in establishing presence of hepatic damage particularly in jaundiced patients However normal prothrombin may

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tomy leaving a portion of the viscus just above the neck or cholecystotomy It is imperative to examine the removed gallbladder immediately and to demonstrate that only the cystic duct has been divided In some cases accident has been recognized only by this examination a portion of common duct usually about 1/2 in long being found attached to the removed gallbladder Immediate repair of the duct is the only permissible course

When injury is not recognized until later repair should not be too long delayed The surgeon is often confronted with a patient who has been jaundiced for a year or so and is bile logged and toxic with the liver enlarged perhaps a handbreadth below the costal margin When jaundice supervenes operation is inevitable and should be undertaken within two or three months of the accident As in other operations on jaundiced patients careful preparation is required If there is any severe degree of red cell fragility the patient should have preliminary transfusion Secondary anemia sometimes requires treatment by transfusion

Turner believes direct implantation of the stump of the common hepatic duct into the duodenum is the best method of repair but a big opening is essential to allow for the contraction which invariably follows This is one of the most difficult of all abdominal operations

[This tragedy usually occurs during the operation for removal of the gallbladder It rarely if ever follows simple drainage of the gallbladder even by the novice. Those who survive the immediate injury are often doomed to a l ring death It is one of the most depressing and difficult conditions which the clinician and surgeon alike have to face —Ed]

Results of Intravital Liver Puncture R Stahel has shown in numerous cases that liver puncture yields clinical data of importance both in diagnosis and in prognosis Comparison of results of puncture with a thicker needle (Roholm and Iverson) with those made with a thinner needle and histologic study in each case shows that although a good picture of the liver cells can be obtained with the latter method the former makes possible ap

(9) Schweiz. med Wchnschr 73 1317 13 1 Oct 30 1943

be found in the presence of liver disease and conversely hypoprothrombinemia resistant to vitamin K may be of nonhepatic origin as encountered in idiopathic hypoprothrombinemia and after administration of dicumarol

Injuries to Main Bile Ducts According to G Grey Turner[8] (Univ of London) such injuries are not rare and often are tragedies About one third of the patients die of the immediate consequences and another third from operative intervention for repair of the injury Although one third make good immediate recoveries after such intervention recurrence of biliary disease may eventually prove fatal Injuries to the main ducts are nearly always surgical and are therefore a serious reproach to surgeons They cannot be regarded as an ordinary risk of gall bladder surgery although accidents occasionally occur Mistakes are easy when the common ducts are so lax that they may be drawn into a loop and inadvertently included in the ligature *Residual inflammation of the sclerosing* type after removal of an acutely inflamed viscus may occasionally occlude the common duct

Distinction must be made between cases in which injury is recognized when the duct is divided and is immediately repaired and cases in which it is not recognized until some time after primary operation In 2 of Turner s 12 cases immediate repair was done 1 patient died just after operation and the other was well five years later Of 10 patients in whom late repair was done 3 died after operation 1 was recovering from a recent operation 1 had recurrent symptoms 8 years after operation and 5 died of recurrent biliary disease after 3 5 5½ 12 and 17 years

Adequate exposure is essential in gallbladder surgery Turner prefers the oblique muscle cutting incision just below the right costal margin The cystic duct should be exposed and isolated first but no clamp or ligature should be applied to what is supposed to be the cystic duct until the common hepatic and common bile ducts are clearly seen When this anatomic disposition cannot be determined satisfactorily the proper procedure is partial cholecystec

(8) Lancet 1 621 62 May 13 1944

more severe forms of liver disease e g obstructive jaundice of long duration There are no characteristic changes in the liver cells in icterus intermittens juvenilis (Meulengracht) In acute yellow atrophy of the liver cellular damage is more marked with greater degeneration of protoplasm and vacuolization and pyknosis and finally complete disappearance of nuclei In obstructive jaundice the liver cells are saturated with bile pigment in large irregular clumps this is usually more marked than in epidemic jaundice In certain cases there are also changes in protoplasm with the melting snow phenomenon as well as changes in chromatin content of nuclei In two cases of hemolytic icterus the liver cells were not changed but there was a fine bluish pigment which did not collect in clumps and which could be differentiated from bile pigment seen in epidemic and obstructive jaundice although its exact nature was not determined

In cirrhosis characteristic changes are bands of fibrocytes and simultaneous fatty degeneration of liver cells In primary carcinoma the liver cells display an enormous enlargement and protoplasm and especially the nuclei contain large vacuoles and nucleoli are abnormally large Chromatin content is altered often increased and often the nuclei are very clear Size of the nuclei shows gross alterations Many cells consist only of a nucleus without protoplasm In the protoplasm itself is occasionally seen a massive accumulation of bile pigment A large number of macrophages are apparent a finding also characteristic of hepatic metastases

Only positive findings have any significance in diagnosis of liver metastases Negative findings do not rule out the presence of metastases since the needle may not have reached a metastatic node Metastases are recognized as nonhepatic polymorphous cell groups

Fibrocystic Disease of the Pancreas is described and clinical and pathologic data on six cases are presented by R I J Kennedy and A H Baggenstoss Infants and children with this disease exhibit many features of celiac disease

(1) P oc S ff M M y C l 18 487 493 D 15 1943

praisal of the reticulum Since however the Roholm Iverson method causes a certain mortality its use is avoided unless there are definite indications for it puncture with a thinner needle causes no complications unless there are definite contraindications such as a hemorrhagic diathesis

Stahel describes the changes observed in hepatic cell

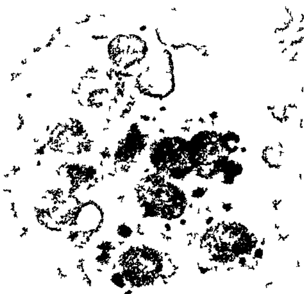


Fig 133 —(p f l ll pider c l ; t t Not ble i cr a e ; g ; t t t w th ; r ; f m ; a nt d t p ph ry

in different liver diseases In epidemic jaundice are found along with normal liver cells a considerable number of cells with greatly increased pigment content and with the protoplasm pigmented even at the periphery (Fig 133) There are occasional cell with multiple nuclei In a few severe cases a grainy protoplasm is evident and pigment is lacking in the outer part of the cell exhibiting the so called *melting snow phenomenon* This la a) o m

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(1) P oc St ff M M y Cl 18 48 493 D 15 1943

such as intolerance of fats and carbohydrates in the diet large foamy light colored foul smelling stools and failure to gain weight and height They also have chronic bronchitis and bronchiectasis They do not improve when treated by accepted dietary methods life expectancy is a few months or year and there are pathologic changes in the pancreas lungs and sometimes other organs Glucose tolerance may be normal or even increased and duodenal



Fig 134—H m t yl n o ed ced f m × 110

contents are devoid of trypsin In some cases the first symptoms are those referable to the respiratory tract persisting for several weeks or months before the celiac syndrome becomes evident Another remarkable feature of fibrocystic disease is its tendency to occur in more than one member of a family

Etiology is unknown Whatever the cause there is loss or destruction of acinar tissue of the pancreas with resultant deficiency of important pancreatic secretions Pathologic changes are irreversible and therefore incompatible with life The greatest age attained by any patient reported in the literature was 14 years The authors patients were aged 21 (two) 2 6 and 5 m [illegible] and 21/

years The first five had died at the time of the report The last two patients in the group were brother and sister Two were only children One patient had three healthy siblings but five others had died before the age of 5 months each of these had had a troublesome cough and diarrhea The remaining patient had one sibling who had died at 6 months with symptoms suggesting fibrocystic disease of the pancreas

Grossly the pancreas presents few recognizable changes In the five cases examined it was impossible to follow the duct of Wirsung with a probe throughout its extent but this is not proof of obstruction if the small size of the duct at this age is considered Histologic appearance of the pancreas varied considerably depending on the developmental stage of the disease In all cases dilated ducts and acini contained varying amounts of coagulated secretion Epithelial lining cells were flattened and occasionally resembled squamous epithelium Secreted material occasionally had a laminated appearance and usually was acidophilic Part of the intra acinar material stained like mucus and part like fibrin suggesting that it was a mucoprotein of some type Interacinar and interlobular connective tissue also increased variably A few lymphocytes and mononuclear cells and an occasional polymorphonuclear cell were observed in interstitial tissue but the predominant cell was the fibroblast In one case the parenchyma had been largely replaced by fibrous connective tissue (Fig 134) and there were only a few dilated ducts and acini This was the most advanced lesion

Gross pulmonary lesions consisted of suppurative bronchitis and bronchiectasis patches of bronchopneumonia and abscesses Histologically bronchi and bronchioles contained abundant purulent exudate and there was much ulceration of epithelium Many bronchioles were dilated and flattening of the epithelium was present in three cases Some fatty change of the liver was present in three cases Small deposits of calcium salts in epithelial cells and lumens of a few convoluted tubules and loops of Henle were observed

Association of Carcinoma in the Body and Tail of the Pancreas with Multiple Venous Thrombi Two cases of carcinoma of the pancreas one of the body and one of the tail are reported by William E Kenney (Washington Univ) In both multiple venous thrombosis was a prominent feature of the clinical and pathologic picture Review of 51 additional cases 30 of the head and 21 of the body and tail disclosed carcinoma of the body and tail associated with multiple venous thrombosis in 33 per cent of the cases while carcinoma of the head of the pancreas showed no such striking association

In attempting to explain this phenomenon various extrinsic and intrinsic factors were considered and found inadequate However these tumors may secrete an abnormal substance or an undue amount of a normal substance concerned in blood clotting an assumption supported by the fact that in every case showing multiple thrombi the tumor is of the mucinous type The mucinous tumors of the pancreas may arise from the ducts Kiefer stated that cylindric epithelial cells are of ductal origin Ewing concurred and mentioned a rare gelatinous change Karsner believed that the cylindric cells arise from the ducts but pointed out the fallacy of such a morphologic comparison when dealing with malignant tumors Possibly the ductal epithelium normal or neoplastic or both elaborates and secretes a substance concerned with the clotting of blood

Total Pancreatectomy for Hyperinsulinism Due to an Islet Cell Adenoma, with survival and cure 16 months after operation is reported by James T Priestley Mandred W Comfort and James Radcliffe Jr[3] (Mayo Clinic)

In a woman 49 total pancreatectomy was followed by a relatively mild diabetes Disturbance of carbohydrate digestion was not detected by methods used to investigate it while digestion of protein and fat was definitely diminished About 35–70 per cent of ingested fat and 25–55 per cent of ingested nitrogen could be accounted for in the feces A

(2) Surgery 14 600 608 October 1943
(3) Ann Surg 119 211 2 1 February 1944

positive nitrogen balance occurred despite large loss of nitrogen in the feces. Food stuff in the urine and feces accounted for 21–34 per cent of calories ingested. Percentage of total fat in the stool as neutral fat varied from 54 to 65 per cent. Dried weight of stools was greater than values obtained for healthy person. The patient has remained in excellent health 16 months after operation. Evidence of lipocaic deficiency has not developed.

A less radical procedure would have failed since the *adenoma was in the head of the gland in intimate proximity to the duodenum.* This is believed to be the first case of total pancreatectomy for benign or malignant disease in which the patient has survived beyond the immediate postoperative period.

Diagnostic Value of Pancreatic Function Tests. Louis Bauman and Allen O. Whipple (Columbia Univ.) determined reaction and ferment concentration of pancreatic juice in nearly 150 patients. This experience with that of Pratt and others indicates that a test of external *function of the pancreas may well become an important* diagnostic procedure. Mecholyl injection induces secretion of a relatively concentrated pancreatic juice well adapted for ferment determination. Separate aspiration of the stomach is necessary to avoid acidification which *injures pancreatic ferments. A tube with two lumens is* used for this purpose.

Functional disturbances of external secretion of the pancreas may occur without demonstrable histologic changes in the organ. In cases of stone in or cancer of *the bile ducts normal pancreatic juice is usually obtained.* Painless obstructive jaundice associated with normal pancreatic juice is usually found in cancer of the bile ducts. With tumor of the ampulla normal pancreatic ferments may be obtained if the pancreatic duct or ducts enter the duodenum *separately or if there is an accessory duct of* Santorini. In only one patient with proved cancer of the pancreas were normal ferments obtained; in this case cancer of the head of the pancreas invaded the common bile duct without obstructing the pancreatic duct. In the series

(4) Am. J. M. S. 81 9 M h 1944

with normal pancreatic ferments no evidence of pancreatic disease was found except in one case in which histologic examination showed a predominantly normal picture with an occasional patch of fibrosis

Painless obstructive jaundice with low or absent pancreatic ferment concentration is almost always due to cancer of the pancreas Pancreatitis is usually associated with pain If pancreatitis is acute elevated serum amylase is the rule this is reliable indication of acute pancreatic disease This ferment is readily excreted by the kidney so that fleeting edema of the pancreas may escape recognition if the test is delayed Alkaline juice is usually present even in advanced pancreatic disease and activity of the three ferments is not affected equally In some patients concentration of one ferment remains normal while that of the other two is markedly diminished

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DISEASES OF THE INTESTINAL TRACT

Nonmeckelian Diverticula of Jejunum and Ileum Raymond E Benson Claude F Dixon and John M Waugh review 122 cases of nonmeckelian diverticula of the jejunum and ileum observed at the Mayo Clinic in 34 years Approximately 200 additional cases are recorded in the literature indicating that such diverticula are not exceedingly rare

Nonmeckelian diverticula of the *small intestine* occur more frequently in the jejunum than in the ileum The jejunum was affected in 100 of the 122 cases in this series In 17 the diverticula were limited to the ileum and in 5 they occurred throughout the small intestine The proximal portion of the jejunum was most frequently affected

These diverticula may occur in any position around the circumference of the bowel however most are situated along the mesentery Sometimes they are actually within the mesentery pushing the leaves of this structure apart

(5) Ann Surg 118 377 393 September 1943

The diverticula vary in size from a few millimeters in diameter to large outpouchings The larger diverticula in this series measured 8–9 cm in diameter Most of the diverticula had an average diameter of 1–4 cm They were in general considerably larger than the usual tiny outpouchings seen in the colon (Fig 135) The openings by which these diverticula communicate with the bowel vary from 1 mm in diameter to large lumens 3–4 cm

When these diverticula are large their walls may be very thin consisting merely of serosa and a thin mucosal layer Small diverticula have thicker walls consisting of the usual intestinal structure In 44 of the 122 cases only 1 diverticulum was observed 37 of these solitary



F g 135 —M n 62 d d f co y thr mb s A t p y pec m n h w m lt pl la g d m ll d t l t bord f j j m

outpouchings occurred in the jejunum and 7 in the ileum Two diverticula were noted in each of 12 cases and in the remaining 66 cases three or more were present Diverticula in other viscera were observed in 49 of 85 cases in which autopsy was performed In only one of these 85 cases did the diverticula in the small intestine represent the probable primary cause of death Diverticula of the intestines were observed incidentally in all the rest They were noted in all age groups

Uncomplicated diverticulosis of the small intestine does not give rise to any characteristic symptoms In five cases of the group in which autopsy was not performed all other abdominal organs were ruled out as possible sources of the presenting symptoms by multiple roentgen and clinical tests The patients all complained of constipation flatulence and abdominal discomfort Abdominal discom

fort varied from mild indefinite abdominal aching to frequent *moderately* severe attacks of pain without definite localization These symptoms were possibly attributable to the diverticula

Uncomplicated and asymptomatic diverticulosis of the jejunum or ileum does not require surgery In evaluation of *symptoms of diverticulosis all other possible causes* of the complaints must be ruled out for the diverticula are usually silent and the patient s distress may be due to an unsuspected disease of the gallbladder stomach or colon *However when acute complications such as intestinal* obstruction diverticulitis or rupture of a diverticulum present themselves surgical treatment is often imperative In operations on such cases it is probably best to limit surgery to relief of the urgent condition

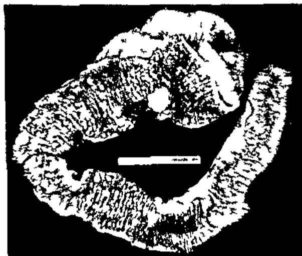
An attempt at surgical elimination of the diverticula is justified when persistent distressing symptoms the syndrome of diverticulosis and chronic obstruction or other chronic complications are present As a rule entero *enterostomy is preferable to resection and anastomosis* in one stage unless the diverticula are localized to a small segment The patients are often poor surgical risks There is also a distinct danger of rupturing one of the fragile *thin walled diverticula during an extensive procedure* A shortcircuiting procedure alone may relieve symptoms If not the involved segment may be resected with less risk at a later date

Carcinoid Tumors (So Called) on the Ileum Malcolm B Dockerty and Frank S Ashburn (Mayo Clinic) reviewed records and pathologic specimens of 130 carcinomas of the small intestine and found 30 so called car*cinoid tumors 13 of which had metastasized locally or* distantly These 13 tumors were in persons in the older age groups and in nine instances were responsible for disabling symptoms chief among which were those indicative *of chronic intestinal obstruction* Preoperative diagnosis of the type of lesion was not possible but radical surgical procedures were carried out in most cases in

(6) Arch. S g 47 2 1 46 S pt be 1943

accord with known results which had followed similar procedures used in dealing with carcinoid tumors Fresh tissue identification of type was of considerable assistance in deciding this issue of treatment Follow up studies ap peared to justify the type of treatment used

The neoplasms tended to be present in the terminal segments of the ileum as small orange submucosal nodules with minimal ulceration (Fig 136) In 50 per cent of cases



Fg 136—S g cal pe m t g f8 d pe d t g d 1 d nocar m d type

in which accurate information was available the tumors were multicentric There was pronounced infiltration of the submucosa muscularis peritoneum nerves lymphatic spaces and blood vessels Puckering and kinking in the region of tumor invasion were observed and may provide a valuable roentgen sign of identification Involvement of regional nodes was observed in 11 and hepatic metastasis in 5 instances Microscopic studies afforded evidence that all carcinoid tumors are in essence peculiar low grade (1 Broders) adenocarcinomas It is suggested however that the word carcinoid be appended by virtue of customary

usage and at the same time perhaps as a designation of the peculiar mode of origin life history and spread

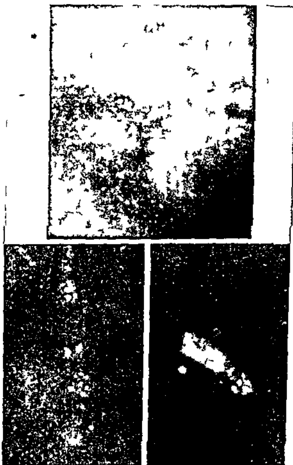


Fig 137 (top) —Stool pe n e f p t t w th ob t ct e j ndice F t dr plets rr gul ly sc tt ed att hed t d b n pl e. *Flu r sc e* pl t m g th t ned w th jh jl 3R × 80
Fig 138 (bott m left) L j men of p t nt w th n pl o is L g ca ta c ta n m y fat l tl t Fl c photom g ph phosph n 3R × 80
Fig 139 (bottom ght) I sp m f p t ent w th neph M y f t d oplets vary g n s Fl gh m c g ph pho thin 3R × 40 (V lk f ep e p 717)

Microscopic Demonstration of Fat in Urine and Stool by Means of Fluorescence Microscopy According to Bruno W Volk and Hans Popper (Cook County Hosp) fat droplets in urine and feces can easily be demonstrated under the fluorescence microscope with a 0 1 per cent olution of phosphin 3R used as a stain This gives much

ESTIMATION OF AMOUNT OF FAT IN FECES DEMONSTRATED BY PHOSPHIN 3R IN 127 PATIENT WITH VARIOUS DISEASES

Clinical Diagnosis	1+	2+	3+	4+	Negative
Obstructive jaundice	5	–	2		1
Cirrhosis	1	–	1		20
Acute hepatitis	3	[illegible]			16
Possible carcinoma of pancreas	3	–	1		4
Peptic ulcer of stomach	3				7
Carcinoma of gastro intestinal tract				1	4
Organic heart disease	4				1[illegible]
Miscellaneous (diabete essential hypertension gastro enteritis pulmonary tuberculos cere bral hemorrhage etc)					21

better results than the sudan III method and is much simpler than the more elaborate method which gives clear pictures (osmic acid) If an ultraviolet light source is available for fluorescent microscopic examination it can be recommended as a simple clinical procedure

Demonstration of fat in feces indicates faulty digestion and absorption of fats as seen in insufficiency of external pancreatic secretion or in disturbance of bile secretion (see Table) Doubly retractile lipoids in urine indicate pathologic permeability of the glomeruli for lipoids as seen chiefly in nephrotic conditions The significance of these findings awaits further observations

Acute Diarrheal Diseases Albert V Hardy and James Watt (Natl Inst of Health Bethesda Md) report studies conducted in four areas representative of those with very high high medium and low mortality from diarrheal diseases (Puerto Rico New Mexico Georgia and New York City) Satisfactory clinical data were

(6) Am J Clin Path 14 34 38 Ap 1 1944
(7) J A M A 124 117 11 9 Ap 1944

CLINICAL AND ETIOLOGIC CLASSIFICATION OF DIARRHEAL DISEASE

G u	CLINICAL ENTITI s	Usu L C u s	SE ERIT	ETIOLOGI A ENT
Ir ma y in fect u	B l y dysentery	Acute	Mild to e y se e	Sh gella dy te a nd S pa ady ei ter a t Sh g Fle n S nn N wc tl (B yd 88) a d S hm t
	Ameb dyse te y	Acut to h on c	Se ere	F l m b h st lyt a
	Food f ct on	V y acut	S	Salmo ll h fly S t rl m t d S e te t d s
	Ch l	V y cute	V	Ch l a v b
	Othe l te ial nf ct	V bl	M l l	St lact t t k p ne l l ne ll n l p cu l m n l j t l
	[illegible]	Va abl	V all	Va hel th d fl k ll t
	[illegible]	A ut	M de t to e ere	Cl fl st pt o c l o t pl ylococ l p e i coc l blv
	T be l e te t	Cl o	S	T t l bac ll
	Ce al d nf t ons	Va bl	V all	Va ble
N fec t o s	Fo l po on g	A t	Mod t t sev	T x p od ic st phyl coc p ll y ther o g n ms
	S wag po son ng	A ute	M H t od te	P od ts of bact al d n po t n
	Nut t o l dia rh a	S ba nte	M l l	D etary lefi i n y and lt to ga t o t t nal tract
	Allerg d ea	Ac te to h ni	Va ble	Var abl
	N rop ych at d sord	Ch	Va ble	V abl
	Oth	Ch n	S ere	L c l uic at e o b t u t l n as th d to n pl m and lymph g an loma um
Unk own use	Ep l c d h f t w bo n	Ac te	S ere	U k wn

Ill t at f a t t s f nk w u

obtained on 1 247 cases and recorded epidemiologic histories on 830 households 8 643 survey fecal cultures were obtained New highly selective culture mediums were used which increased reliability of bacteriologic findings

A clinical and etiologic classification of diarrheal diseases is shown in the table Primary infectious diarrhea is caused by pathogens which establish themselves and grow in the enteric tract Various organisms are known to be responsible and others are suspected In parenteral and secondary diarrhea the gastro intestinal disturbance is but one part of a symptom complex Genesis of the diarrhea that frequently occurs with acute infectious diseases paranasal sinusitis and some other localized infections is not clear Acute noninfectious diarrhea is commonly caused by ingestion of toxic or irritating substances usually food in which staphylococci or other organisms have grown Water heavily polluted with bacterial decomposition products or industrial wastes is involved less frequently Allergic and neuropsychiatric disorders and nutritional deficiencies may cause episodes of diarrhea usually chronic Dietary indiscretion is blamed rightly in some cases Various chemical compounds including cathartics also may cause noninfectious diarrhea

The cause of diarrheal disease varies with area season and age of persons concerned Statements as to cause must be qualified and limited not generalized

Shigellae are usually transported through movements of infected persons (who are more numerous than has been supposed) chiefly with few or no symptoms Within the household and within larger groups living together organisms are passed rather directly from person to person Prevalence of cyst carriers of Endamoeba histolytica has been reported repeatedly but clinical infection acute or chronic is comparatively rare Exceptionally the organism assumes the role of a highly invasive and destructive parasite most commonly it is seemingly innocuous This striking difference in host parasite relationship is the outstanding problem in epidemiology of this condition and also in others Salmonella infections concerned in diar

rheal diseases ordinarily come from animal rather than human sources reaching man in inadequately cooked meats and eggs and in food soiled with droppings of mice and rats Parenteral diarrhea is distinctive in its seasonal distribution which coincides with that of acute respiratory infections Outbreaks of staphylococcic food and sewage poisoning are highly explosive and ordinarily begin and terminate within 24 hours

An outstanding observation in 555 patients whose stools were culturally positive for one or another variety of shigella was the wide variation in severity of disease There was a full range of clinical types from just a few loose stools to fulminating rapidly fatal illnesses General population surveys also revealed many asymptomatic carriers of shigella The commonest clinical manifestation was simple diarrhea Abdominal pain anorexia nausea vomiting and weakness were reported in that order of frequency Fever when present was usually an early manifestation at times preceding and overshadowing diarrhea especially with shigella of the Sonne or Schmitz variety Less common symptoms were tenesmus dehydration loss of weight convulsions in children and chills in adults Bloody dysenteric stools were infrequent even in severe cases with positive fecal cultures Most diarrhea due to shigella terminated spontaneously with clinical recovery in a week in adults usually in two to four days Illness in infants was more prolonged and all 39 fatalities were in children under 2 Amebic dysentery cannot be differentiated from bacillary infection on clinical grounds alone Generally clinical amebiasis has more gradual onset slower evolution and greater tendency to chronicity With acute symptoms the stools are commonly bloody

Differential diagnosis of endemic acute diarrheal diseases can be made definitely only by isolation of specific etiologic agents Since this involves delay and since specific chemotherapeutic agents should be given promptly satisfactory working diagnoses are needed As a first requirement the most probable diagnosis in the particular area and group must be known It must be appreciated that varieties

of shigella prevailing in this country rarely cause the severe dysentery described in medical texts Shigella paradysenteriae infection is the most probable diagnosis for endemic acute diarrhea in older children and adults particularly during warm seasons and in younger children and infants in the South and Southwest Other causes such as parenteral infections and dietary factors appear more commonly in early infancy Amebic dysentery is to be considered when persisting acute usually bloody diarrhea occurs sporadically Acute diarrhea caused by salmonella cannot be differentiated clinically from that due to shigella the former tends to produce higher fever more vomiting greater abdominal tenderness and less blood in the stools Food poisoning due to staphylococcus is characterized by a brief and stormy course with distressing vomiting severe diarrhea and little if any fever

Management consists of control measures to prevent spread of infection through personal hygiene and public sanitation and use of sulfonamides in treatment and in control especially of shigella infections

Frequency of Bacillary Dysentery at Cook County Hospital is reported by F F Chesley and C I Woolsey When careful clinical and laboratory studies are made of all patients with dysentery diarrhea and enteritis incidence of unclassified dysentery decreases as the diagnosed cases of bacillary dysentery increase Bacillary dysentery occurs in Chicago as a sporadic disease throughout the year with greater frequency in late summer and autumn From 1938 to 1941 507 cases were diagnosed at Cook County Hospital To establish the diagnosis the causative organism must be isolated and identified

Some patients harbor the organism over extended periods in this series as long as 70 days These patients may be considered carriers Mortality in this series was 7 per cent Most deaths occurred among the aged with complicating diseases and the very young

No routine treatment was carried out especially among the adults Saline and glucose solutions were administered

C I oe t I gy 258 64 Ap I 1944

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alone in this area are six times greater than the casualties directly attributable to military operations —Ed]

Treatment of Asiatic Cholera with Sulfaguanidine Joo-e Huang[2] (Kweilin China) report a study of 22 cases Adults received 3 Gm as a first dose 1 Gm every two hours for six doses then 1 Gm every four hours for a day or two A boy 11 received 2 Gm initially and maintaining doses of 0 75 Gm A girl 6 received 1 5 Gm at first and 0 5 Gm as a maintaining dose Patients were ordered to drink as much water as possible and circulatory stimulants such as camphor water and tincture of digitalis were given repeatedly subcutaneously or orally No other drugs were administered Treatment was started 4-24 hours after onset All patients showed typical symptoms of cholera vomiting severe rice water stool muscular cramps and diminution in both amount and frequency of urine even anuria Some were in collapse but severity of dehydration varied Improvement was noted three to four hours after administration of sulfaguanidine vomiting and diarrhea almost ceased cyanosis disappeared and secretion of urine commenced or increased with concomitant improvement in general condition Eight hours after treatment stool cultures were negative for *cholera vibrio*

Twenty one patients recovered promptly one died 73 hours after onset Reported mortality is 20-60 per cent

[The fact that a war of global proportions makes possible at least the introduction of cholera carriers enables one to derive considerable comfort from Huang's favorable results Penicillin also exerts bactericidal effect on Vibrio comma —Ed.]

Treatment of Bacillary Dysentery Carriers Robert J Hoagland Frank H Harris and Richard B Raile report that bacteriologic examinations of feces of patients who had had bacillary dysentery and of their contacts resulted in the detection of 45 carriers (32 chronic) of Shigella paradysenteriae

Sulfaguanidine was given to 30 and succinylsulfathiazole to 15 in a daily dose of 20 Gm divided into four portions given between 8 00 a m and 8 00 p m and administered for six days Bacteriologic examination of

(1) J A M A 125 23 4 May 6 1944
(2) W Med. 4 400 403 Oct be 1 43

for dehydration when indicated Bismuth and opium were used most frequently for abdominal pain Prompt ad ministration of fluid to all pediatric patients produced striking improvement and undoubtedly accounted for the low mortality (4 per cent) among infants Sulfaguani dine or other sulfonamides were not administered rou tinely in enough cases to justify deductions as to their therapeutic value

Dysentery in American Troops in the Middle East Charles W Wirts Jr and Edward J Tallant[9] (M C A U S) report on examination and cultures of 1 298 stool specimens in a general hospital for American troops in the Middle East Three hundred specimens from 200 American soldiers classified as food handlers 50 Suda nese soldiers and 50 native workmen selected as a con trol group showed that the American soldiers did not have a high carrier rate for either amebas or bacillary dysentery organisms The *native workmen did not have* a high carrier rate for bacillary dysentery but almost all of them showed some form of intestinal parasitic infesta tion

Approximately 12 per cent of the patients examined har bored at least one form of intestinal parasite 23 per cent showed a bacillary pathogen in the stool The predominant pathogen was Flexner s bacillus which showed consider able seasonable variation in incidence All patients received sulfaguanidine or sulfathiazole and all recovered satisfac torily That few were seriously ill is probably attributable partly to early administration of sulfonamides and lack of *epidemic proportions of the disease owing to mainte* nance of a high standard of hygiene

Of all patients whose stools revealed no pathogen only 10 per cent had symptoms exclusively attributable to dysentery

[On the Burma front where because of terrain climate and absence of means of communication military operations are undertaken with difficulties unsurpassed by those of any other fighting front, military authorities recently have stated that the mortality and morbidity re ulting from malaria and dysentery

(9) Am. J D g t. D 11 252 255 A g t. 1944

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(1) J. A. M. A. 125: 3-24, May 6, 1944
( ) W. M. J. 4: 400-403, Oct. 1943

feces was resumed four days after cessation of treatment Both SS agar and desoxycholate citrate agar (including 5 mg para aminobenzoic acid in each 100 cc) were used for feces cultures material for which was obtained from feces rectal swabs or both Each patient had one feces examination after administration of magnesium sulfate The minimal number of post treatment feces specimens secured for culture from a single patient was 9 the maximal number 15 and the average 11 In all 503 feces cultures were examined

Dysentery bacilli disappeared from the feces of every patient No significant toxic reactions attended the use of either drug but the patients receiving succinylsulfathiazole experienced minor annoyances The criterion of cure was a minimum of nine consecutive negative reports of feces cultures made from the fourth day following cessation of treatment Use of rectal swabs as a source of feces for culture is convenient and practical and results in securing a higher percentage of positive reports than the use of excreted feces

Studies on Transmission of Amebiasis in a Children's Home in New Orleans The continued high incidence of amebiasis in a children's home over a period of many years afforded Grace Louise Ivanhoe[3] (Tulane Univ) the opportunity of studying the mechanism of transmission of amebiasis in an institutional environment By use of the Foerst centrifuge and NIH swabs Endamoeba histolytica was isolated from hands and soiled underwear of the children bottom of the laundry chute damp sand in the play box wading pool contents and concrete floor of the pool after draining Other parasites were also found in these and other places

Since the continued high incidence appeared to be due to direct contact transfer and general pollution of the environment the home was cleaned throughout with live steam at the same time that mass chemotherapy directed against Endamoeba histolytica was carried out on the attendants and children The efficacy of steam sterilization

(3) Am. J Trop Med 3 401 419 July 1943

as a supplementary means of eradicating the infection extrinsically was later tested by using NIH swabs in locations previously contaminated. Four weeks after completion of treatment, examination of one stool specimen from each child by means of the direct fecal film and zinc sulfate centrifugal flotation technic showed not a single positive specimen.

These tests indicate that use of live steam to sterilize the environment together with antiamebic mass chemotherapy constitutes a simple and practical means of controlling amebiasis.

Lambliasis Intestinalis. E. F. Rissmann (Krakow) reports that in his hospital routine duodenal aspiration in all patients with gastro-intestinal disturbances disclosed that lambliasis was about as common as bacillary dysentery. There were 26 cases of lambliasis during a period when 25 cases of bacillary dysentery were seen. The largest number of cases occurred during the period when lettuce and radishes were most plentiful.

Rissmann does not consider *Lamblia intestinalis* a harmless parasite. An alkaline milieu greatly favors its development; it flourishes in the duodenum, particularly when gastric aspiration reveals anacid or subacid values. Eight patients had no free hydrochloric acid, 12 subacid values, 5 normal acidity and 1 hyperacidity. There are three types of lambliasis—gastro-intestinal, cholangitic hepatic and cachectic—and one develops chronologically from another if treatment is not instituted early.

Acridine dye derivatives such as atabrine and acranil are most effective in treatment; therapeutic progress should be controlled by doudenal aspiration. Usual hygiene for any intestinal infection should also be observed. Duodenal aspiration should be carried out in every patient with persistent epigastric disorder, particularly with weight loss and jaundice. Duodenal juice must be examined promptly because lamblias do not remain viable for long. Early treatment prevents parenchymal hepatic lesions.

[Texts and monographs extolling the benign virtues of this

(4) M d Kl 38 532 533 I 5 194

parasite require early revision The clinical manifestations of thi particular infestation and the viability of the organism after a piration need to be borne in mind —Ed.]

Syndrome of Symptomatic Sprue with Lymphosarcoma of the Small Intestine and Mesenteric Lymph Nodes Robert Fritzsche reports a case

Man 45 had chronic diarrhea with stools consisting mostly of neutral fat but containing some fatty acid crystals abdominal distention severe emaciation and secondary anemia with color index 1 0 Diagnosis of endemic sprue was based on these findings and the roentgen examination which suggested severe jejunitis ileitis and colitis Blood studies to determine whether there was hypocalcemia with osteoporosi due to disturbance in calcium metabolism were not made. There was no evidence of tetany or abnormal pigmentation as in many cases of sprue with Addison s disease and blood pressure levels argued against adrenal insufficiency The patient survived five months after first appearance of symptoms

Autopsy showed advanced lymphosarcoma of the jejunum and upper ileum of the lymphoblastic type. There were numerous small and large lymphosarcomatous nodes the larger ones usually showing ulceration and erosion of small blood vessels in the ulcerated portion of some of the nodes There was marked bleeding in the intestine. High grade lymphosarcoma was noted in the mesenteric retroperitoneal pancreaticoduodenal and para aortal lymph nodes and also in the left iliac and bilateral inguinal nodes the upper cervical on both sides and one paratracheal node on the right There were moderate ascites and subchronic inflammation of the jejunum and upper ileum

Fritzsche concludes that correct diagnosis should have been possible in view of certain observations not characteristic of endemic sprue Among these were the rapid course as contrasted with the usual chronicity of sprue and absence of certain symptoms of the sprue syndrome such as tetany and pigmentation Also studies of calcium metabolism and biopsy specimens were not made and the roentgen findings were difficult to interpret Furthermore there was neutral fat in the stools whereas in sprue fatty acid crystals predominate

This experience shows that diagnosis of sprue should not be made on the basis of suggestive symptoms without

(5) Schw z. med. W nschr 73 44 445 Ar 10 19

careful investigation of possible pathogenic factors Correct diagnosis is of great importance since prognosis for sprue with proper treatment is generally favorable Failure of the usual methods in the presence of lymphosarcoma of the small intestine would be expected

[Obscure abdominal complaints with or without associated diarrhea and puzzling cases of undernutrition are often cleared up when the possibility of steatorrhea is borne in mind or actually determined Then the question arises whether the excess fecal fat is due to sprue pancreatic disease or a granulomatous state of the small bowel such as chronic jejuno-ileitis or is the result of extensive disease of the mesenteric lymph nodes interfering with absorption In classic types of these various disorders the clinical picture roentgenologic findings in the small intestine tests of pancreatic function employing a suitable stimulus and the double lumen tube and other laboratory findings usually lead to the correct diagnosis But in mild atypical or borderline cases differential diagnosis can prove exceedingly difficult —Ed]

Studies on Human Schistosoma Mansoni Infections *Proctoscopic Picture in Asymptomatic Schistosomiasis* Z T Bercovitz R Rodriguez Molina Dudley W Hargrave J D Dickie and Charles E Green (M C A U S) found ulcerations of the rectal mucosa in 60 7 per cent of 155 otherwise healthy Puerto Rican young men in whom ova of Schistosoma mansoni were discovered on routine fecal examination The mucosa was generally soft velvety and pale pink with single or multiple pinpoint or linear ulcerations There was sharp demarcation of the ulcerated area from the surrounding normal mucosa and no zone of inflammation no crater or ragged edges and no exudate The ulcerations were noninflammatory breaks in the continuity through which oozed a small amount of blood situated at the bifurcation of the capillaries or lying directly on them and showing a definite relationship to the blood vessels When the ulcerations were numerous they outlined the pattern of the capillaries Polyps were seen in only two instances

A review of present concepts of schistosomiasis as pointed out by Faust Strong Koppisch and others in clinicopathologic studies fails to account for this large group of infected persons with definite pathologic find

(7) J A M A 1 5 9 1 9 6 1 A g 5 1941

ings in the rectal mucosa but without clinical symptoms Schistosomiasis must be considered in any person who has lived in a geographic area suspected of harbor g Schistosoma mansoni It must be ruled out by careful repeated examinations of the stools even though no symptoms are present Presence of Schistosoma mansoni indicates schistosomiasis There is no such thing as a healthy carrier of schistosomiasis

[Schistosoma man oni may also g ve rise to extensive visceral changes in either a frank or an insidious fashion Examination of a freshly passed fecal specimen after saline purgation should be carried out as routine in patients or discharged soldiers who have resided in infected areas We have also found it very necessary to carry out such routine examination for the common parasites and their ova in patients residing in the Carribbean littoral The degree of infestation is surprisingly high considering the favorable social and economic status of most of such patients —Ed]

Indigestion Due to Constipation. Walter C Alvarez (Mayo Clinic) says that it is not always enough that the physician diagnose functional indigestion Often he must go further and decide what type of functional trouble it is and what mechanism underlies the symptoms A fairly common but insufficiently recognized cause of puzzling indigestion is constipation In an insensitive person a week long stagnation of feces in the colon may not produce any distress but in a highly sensitive woman annoying symptoms may follow in 6–24 hours after rectum has failed to empty itself properly Presence of an irritating plug of feces in the rectum will cause back pressure in segments of bowel farther orad with flatulence bloating lo of appetite mild nausea a sort of hunger pain relieved temporarily by eating sense of fulness in the epigastrium headache mental dulness a sense of being poi oned regurgitation or rarely vomiting

Diagnosis often can be made instantly on learning that all symptoms disappear immediately after purgation In other cases laxatives cause so much abdominal distress that this cancels out the benefit that would otherwise come from emptying the colon Actually in some con

(8) Ga t oente ol gy 4 7 431 J 1944

stipated persons most of the symptoms are due to taking too many laxatives or to poor choice of laxative agents This can be demonstrated by having the person stop for a time all measures designed to empty the colon except perhaps a daily enema of physiologic salt solution if the patient recovers little doubt need remain as to the diagnosis Indigestion due to constipation may be present even when the patient is having several small hard bowel movements a day

Constipated patients often have a hypersensitive bowel and hence unwise use of laxatives or rough diets may cause as much flatulence and abdominal distress as was being caused by stagnation of the feces Bulk producing laxatives may be particularly harmful in some cases be cause while they may eventually give the patient one or more bowel movements a day they still may leave the colon more distended than it was before Alvarez believes that for patients with indigestion due to constipation the best way to empty the colon is usually with a daily enema of physiologic salt solution

DISEASES OF METABOLISM AND NUTRITION

Experimental Diabetes An editor observes that hyaline changes are now generally considered the most characteristic pancreatic lesion in human diabetes mellitus and that the condition of the islets in animals with long standing diabetes induced by a short series of pituitary injections may be regarded as analogous with that in human diabetes

Dunn and his colleagues have shown that intravenous administration of alloxan to rabbits can cause acute necrosis of almost all the islet tissue of the pancreas Now Dunn and McLetchie show that when islet lesions are induced in the rat by a series of injections of alloxan hyperglycemia glycosuria and often the cardinal symptoms of persistent and severe diabetes mellitus develop These findings are obviously of great importance but their physiologic significance is not clear

This is the first example of a diabetic condition in which the death of the islet cell can be observed so to speak on the table The rapidity with which selective necrosis can take place is one of the most striking facts now brought out Taking into account the hypoglycemic phase Dunn and his colleagues suggest that alloxan stimulates islet activity and that the cells finally fail and undergo necrosis because they have been overdriven Certainly the histologic picture of the islets is different from that of the pancreatic remnant in Allen s partially depancreatized dogs in which the degenerative changes were attributed by Allen to over stimulation a conclusion recently supported by Best The hydropic degeneration and degranulation in the beta cells which follow administration of diabetogenic pituitary extract to dogs are likewise ascribed by Best and his colleagues to overwork but Houssay s group concludes that the pituitary extract directly induces degenerative changes in the islets and that

(9) *Lancet* 2 389 390 Sept 5 1943

hyperglycemia produced by other means aggravates the lesions arising from this direct action Most other workers have assumed that islet damage is more likely to result from overstrain due to a high blood sugar level but Houssay by continuous intravenous infusion of glucose maintained the blood sugar of normal dogs for four days at the level found in dogs made diabetic by daily injection of pituitary extract and found that the islets showed none of the lesions seen in the pituitary treated dogs the beta cells were hyperplastic rather than degenerate and there were signs of hyperfunction Houssay concludes that the pituitary extract must have a direct action on the islet cells which is not mediated by hyperglycemia The nature of such an action is not clear but Dunn s observations on the extraordinary action of the simple substance alloxan may well offer a new approach *to this problem and ultimately to the problem of genesis* of human diabetes mellitus

Effect of Glucose Administration in Diabetic Acidosis was studied by Howard F Root and Thorne M Carpenter (Boston) who measured oxygen consumption and respiratory quotient in three cases

In diabetic coma administration of glucose solution either intravenously or orally does not result in an increase in respiratory quotient thus indicating no increase in carbohydrate combustion Insulin produces an increase in carbohydrate combustion indicated by a rise in respiratory quotient Even with insulin administration there is no evidence that more than 10 Gm carbohydrate can be or need be oxidized per hour to reduce rate of fat metabolism and so to check process of ketone body formation It is important to remember that the rate of utilization of injected or ingested glucose in the normal individual is low in the resting state only between 6 and 12 Gm per hour is oxidized

The harmful effect of glucose may be concealed in early diabetic coma by the favorable effects of insulin simultaneously administered moderate coma may be converted

(1) Am J M S 0c 34 43 A g 1941

DISEASES OF METABOLISM AND NUTRITION

Experimental Diabetes An editor observes that hyaline changes are now generally considered the most characteristic pancreatic lesion in human diabetes mellitus and that the condition of the islets in animals with long standing diabetes induced by a short series of pituitary injections may be regarded as analogous with that in human diabetes

Dunn and his colleagues have shown that intravenous administration of alloxan to rabbits can cause acute necrosis of almost all the islet tissue of the pancreas Now Dunn and McLetchie show that when islet lesions are induced in the rat by a series of injections of alloxan hyperglycemia glycosuria and often the cardinal symptoms of persistent and severe diabetes mellitus develop These findings are obviously of great importance but their physiologic significance is not clear

This is the first example of a diabetic condition in which the death of the islet cell can be observed so to speak on the table The rapidity with which selective necrosis can take place is one of the most striking facts now brought out Taking into account the hypoglycemic phase Dunn and his colleagues suggest that alloxan stimulates islet activity and that the cells finally fail and undergo necrosis because they have been overdriven Certainly the histologic picture of the islets is different from that of the pancreatic remnant in Allen s partially depancreatized dogs in which the degenerative changes were attributed by Allen to overstimulation a conclusion recently supported by Best The hydropic degeneration and degranulation in the beta cells which follow administration of diabetogenic pituitary extract to dogs are likewise ascribed by Best and his colleagues to overwork but Houssay s group concludes that the pituitary extract directly induces degenerative changes in the islets and that

(9) Lancet 389 390 Sept 25 1943

hyperglycemia produced by other means aggravates the lesions arising from this direct action Most other workers have assumed that islet damage is more likely to result from overstrain due to a high blood sugar level but Houssay by continuous intravenous infusion of glucose maintained the blood sugar of normal dogs for four days at the level found in dogs made diabetic by daily injection of pituitary extract and found that the islets showed none of the lesions seen in the pituitary treated dogs the beta cells were hyperplastic rather than degenerate and there were signs of hyperfunction Houssay concludes that the pituitary extract must have a direct action on the islet cells which is not mediated by hyperglycemia The nature of such an action is not clear but Dunn s observations on the extraordinary action of the simple substance alloxan may well offer a new approach to this problem and ultimately to the problem of genesis of human diabetes mellitus

Effect of Glucose Administration in Diabetic Acidosis was studied by Howard F Root and Thorne M Carpenter (Boston) who measured oxygen consumption and respiratory quotient in three cases

In diabetic coma administration of glucose solution either intravenously or orally does not result in an increase in re piratory quotient thus indicating no increase in carbohydrate combustion Insulin produces an increase in carbohydrate combustion indicated by a rise in respiratory quotient Even with insulin administration there is no evidence that more than 10 Gm carbohydrate can be or need be oxidized per hour to reduce rate of fat metabolism and so to check process of ketone body formation It is important to remember that the rate of utilization of injected or ingested glucose in the normal individual is low in the resting state only between 6 and 12 Gm per hour is oxidized

The harmful effect of glucose may be concealed in early diabetic coma by the favorable effects of insulin simultaneously administered moderate coma may be converted

(1) Am J M Sc. 0(34 43 A g t 1943

into severe coma requiring excessive insulin dosage In advanced coma glucose administration may precipitate the final stage of anuria

The object of treatment in diabetic coma is to re tore normal utilization of carbohydrate by administration of requisite insulin By this means excessive glucose in blood and tissue fluids is oxidized or stored liver glycogen is replenished and excessive ketosis is reduced by a reduction in the rate of total metabolism and of fat oxidation

Insulin Resistance Role of Immunity in Its Production On the basis of a study of six diabetic patients resistant to insulin with examination of their blood for insulin antibodies Jacob Lerman[2] (Harvard Univ) states that antibodies to insulin appear to be antihormonal Insulin resistance is dependent on appearance and concentration in the body of antibodies to insulin Return of normal insulin sensitivity is dependent on disappearance of the immune response Repeated administration of insulin rather than its omission offers a means for overcoming insulin resistance Antibodies to insulin simulate antibodies to other hormones by being hormone specific rather than species specific In patients recovering from insulin resistance the diabetes usually becomes severe requiring 50–60 units of insulin daily Lerman suggests that this represents the level of complete diabetes

Factors Influencing Return of Tolerance for Glucose in Middle Aged Obese Diabetics are discussed by Milton Burt, Handelsman (M C U S A) and David Schultz[3] (Brooklyn) When obese patients over 40 first have glycosuria and hyperglycemia they should be treated by rigid dietary restriction directed toward reduction of weight elimination of glycosuria and production of physiologic blood sugar level With this treatment there may be remarkable return of tolerance for carbohydrate Careful co-operation in following the diet is needed

Diabetes must be diagnosed early in such patients because if weight is lost by neglect in treatment ability

(2) Am J M Sc 07 354 360 Ma h 1944
(3) Ib d. 08 15 4 J ly 1944

to regain tolerance for carbohydrate becomes impaired Response to treatment in such patients is still good particularly when protamine zinc insulin is used Obese patients who neglect treatment for many years and remain obese lose ability to regain their tolerance They become difficult to treat and diet therapy seems of little value Their blood sugar levels remain elevated even with insulin Patients who neglect treatment for many years and who eventually lose weight also show diminished tolerance but management of the deranged glucose economy is less difficult than in those who remain obese

Radioactive Iron Absorption by Gastro Intestinal Tract Influence of Anemia, Anoxia and Antecedent Feeding Distribution in Growing Dogs is reported by P F Hahn W F Bale J F Ross W M Balfour and G H Whipple (Univ of Rochester) Iron absorption is a function of gastro intestinal mucosal epithelium little is absorbed in the normal nonanemic dog but chronic anemia due to blood loss increases absorption perhaps 5–15 times normal In general the same differences are observed in man Change from normal to severe anemia in 24 hours does not significantly increase iron absorption As days pass new hemoglobin is formed body iron stores are depleted and in seven days iron absorption is active even when the red cell hematocrit value is rising Anoxemia of 50 per cent normal oxygen concentration for 48 hours does not enhance iron absorption in this respect it resembles acute anemia Ordinary doses of iron given one to six hours before radio iron cause some mucosa block i e less of the latter is absorbed than anticipated Many variables which modify peristalsis come into this reaction Iron given by vein some days before does not appear to inhibit absorption

Plasma radio iron curves vary greatly They may show sharp peaks in one to two hours when iron is given in an empty stomach but after six hours when it is given with food Duration time of curves also varies widely plasma iron returning to normal in 6–12 hours Gastric duodenal

(4) J Exper Med 78 169 188 Sept 1 1943

or jejunal pouches all show active absorption of iron The plasma concentration peak may reach a maximum before the solution of iron is removed from the gastric pouch another example of mucosa block

Absorption and distribution of radio-iron in the body of growing pups gives suggestive experimental data The spleen heart upper gastro-intestinal tract marrow and pancreas show more radio-iron than expected The term physiologic saturation with iron may be applied to gastro-intestinal mucosal epithelium and explain one phase of acceptance or refusal of ingested iron Desaturation is a matter of days not hours whereas saturation may take place in one or two hours This change is believed to be part of the complex protein metabolism of the cell

Clinical Significance of the Plasma Vitamin A Level Hans Popper and Frederick Steigmann (Chicago) base their conclusions on the literature and 2 673 vitamin A determinations in 454 adults

Under physiologic conditions and with normal nutrition the vitamin A level is constant at certain times of the day and on consecutive days Aberrations of this level therefore assume significance In liver disease the level is sharply lowered often to zero The reduction parallels the degree of liver damage and not the degree or type of jaundice During recovery the plasma vitamin A returns to normal or even higher levels Therefore vitamin A determination may help in the diagnosis and prognosis of liver disease The reduction is due partly to impaired intestinal absorption and partly to disturbed release of vitamin A from the liver both in turn depending on the degree of liver damage In infection the plasma vitamin A level is reduced especially in lobar pneumonia zero levels being found usually during the toxic stage Repeated determinations of the level are of prognostic value The plasma vitamin A level is also lowered in such other conditions as anemia and gastro intestinal carcinoma especially in severely sick patients Reduction of the level in the latter disease renders it a nonspecific index of the

(5) J A M A 123 1108-1114 Dec 25 1943

general condition In renal disease the vitamin A level is often much increased Hypovitaminemia A may develop rapidly in this country it is more commonly caused by processes within the body than by faulty nutrition

Parenterally Administered Amino Acids as Source of Protein in Man. Recent experiments have shown that the 10 amino acids believed essential for growth of rats and for formation of plasma proteins in dogs when administered intravenously or subcutaneously replace all or nearly all the dietary protein required by man for nitrogen equilibrium or retention and that their parenteral administration supplemented with glycine is well tolerated by man These observations point to a valuable means of restoring or maintaining body protein in a diseased or injured person Protein depletion is a serious complication that frequently goes unrecognized until it is far advanced It predisposes to such hazards as lowered resistance to infection and intoxication and impaired healing of wounds In many forms of illness or injury dietary intake of protein is reduced or at best normal whereas need for it usually is increased Reduced appetite or impaired capacity for ingesting retaining or absorbing protein may cause inadequate intake

S H Bassett R R Woods I W Shull and S C Madden (Rochester N Y) report study of a patient 63 with gastrojejunocolic fistula who was given solutions of amino acids essential for growth of rats (see Table) intravenously and subcutaneously without clinical disturbance and with satisfaction of requirements of nitrogen equilibrium and formation of body protein Administration was divided into nine periods of five days each and one the fifth period of three days Between periods 4 and 5 was an 18 day interval during which subtotal gastrectomy was performed Mixture Vb was given during the first three periods with addition of mixture Vn during periods 2 and 3 During period 4 no parenteral treatment was given and nitrogen intake was inadequate with nitrogen loss of at least 10 7 Gm Period 5 began 10 days after

63 [illegible] Med 34 396 408 [illegible] 1944

operation the patient received a soft diet and a good positive nitrogen balance was obtained Parenteral administration of mixture VII was resumed in period 6 with oral feedings of a diet containing chiefly carbohydrate and fat Over 80 per cent of nitrogen intake was from amino acids and there was satisfactory retention In periods 7 and 8 mixture IX was given and caloric intake was increased More nitrogen was retained and the patient gained over 6 lb During the periods 9 and 10 intake

Composition of Amino Acid Mixtures

Amino-Acid	VII Gm	VIII Gm	IX Gm
dl threonine	7	7	7.4
dl valine	8	8	11.1
dl leucine	15	15	22.3
dl-isoleucine	7	7	10.4
l(+)-lysine hydrochloride	15	15	11.1
l(−) tryptophane	2	2	3.7
dl phenylalanine	5	10	11.1
dl methionine	6	6	5.9
l(+) histidine hydrochloride	3	3	3.7
l(+) arginine hydrochloride	5	5	5.9
Glycine	27	25	7.4
Totals	100	103	100.0

of nitrogen was entirely from food Follow up three weeks later indicated continued improvement in general health and rapid gain in weight

This study indicates that when sufficient calories are provided nitrogen obtained from amino acid mixtures is well utilized It should not be concluded that nitrogen from natural foods is better utilized because (1) the mixtures used may not be optimal (2) over 20 per cent of nitrogen contained in them was in unnatural isomers not usable by rats for growth (3) the patient obviously was in better condition at the end of period 8 than at the end of period 6 during which the second course of amino acid solutions was begun and it may be argued that his metabolism was more efficient at the end of period 8 thus giving a certain advantage to periods 9 and 10 during which natural food protein was tested

Plasma protein averaged 5 Gm per 100 cc during periods 1–3 and rose to [illegible]6 Gm during [illegible] 8 Of

urinary nitrogen the amount not excreted as urea and ammonia was higher during periods of amino acid injection than during the period of comparable nitrogen intake from food This apparently is a function of the route of administration and not of the type of nitrogen for it is not present in dogs when the same amino-acid mixture is given by mouth

Glycine was originally added with the hope that it might furnish amino nitrogen for in vivo synthesis of other nonessential amino-acids Experiments in dogs show that this hope is largely unrealized but that glycine somewhat improves tolerance to parenteral administration of amino acid solutions

The study demonstrates the therapeutic value of a synthetic mixture of pure amino acids administered parenterally but does not prove that this mixture contains all amino-acids required by man At all times nitrogen of unknown amino acid composition was consumed and oral diets used by other workers testing amino acid requirements of man contain 5–10 per cent of such nitrogen In another patient amino acid solution similar to mixture Vx provided a positive nitrogen balance for a five day period when it was the only source of exogenous nitrogen

Digestion and Metabolism in High Altitude Flights V V Streltsov discusses the effects of anoxia observed on animal and human material in the altitude chamber at the All Union Institute of Experimental Medicine

Interference with salivary function is the first change noted and the function is the first to be restored Marked changes occur in motor activity of the stomach with complete abolition of the cycles at high altitude Periodicity is restored by giving oxygen at high altitude or dropping to ground level Severe anoxia inhibits secretion by the glands of both Pavlov and Heidenhain pouches but with less severe anoxia such inhibition is observed only in the Pavlov pouch If animals receive oxygen at baro

(7) Mop pt 10 3 13 1941 Am R So t M d. 1 130 139

metric pressure gastric secretion is restored Human subjects showed analogous changes The quantity of lactic acid in the gastric contents increases appreciably during anoxia Little is known of the changes that take place in the pancreas and doudenum However during an expedition to Mount Elbrus it was noted that secretion of sodium bicarbonate by the pancreas increased at high altitude During the first two to six hours at an altitude of 6 000–8 000 meters there are persistent reduction in the quantity of bile flowing from the gallbladder into the intestine and increase in its viscosity and its organic solids including bile acids and bilirubin but a decrease in cholesterol These changes slowly disappear in the recovery period Although intestinal motility does not show much change secretory and excretory functions are markedly disturbed

From the effects of anoxia on the secretory excretory and motor functions of the gastro intestinal tract it may be concluded that both meal schedule and composition of food are important to flying personnel Since emptying of the gastric contents is markedly prolonged in anoxia meals must be so arranged before flights that the stomach will be empty at the time of ascent

As to the effect of anoxia on metabolism carbohydrate tolerance is increased and increased carbohydrate intake greatly improves high altitude tolerance Fat metabolism is disturbed and carbohydrates are needed in greater quantities to compensate for the deficiency Protein metabolism also suffers changes which make caution with protein intake advisable

A great deal of work is still needed in the field of rational nutrition of high altitude flyers Suitable changes in the diet may alter all the changes which take place in the glands of the gastro-intestinal tract and simultaneously prevent changes undesirable for the organism Despite insufficient information what is known permits recommendations that flying personnel use a large amount of carbohydrate in a readily soluble and assimilable form keeping in mind the unpleasant effect of a ount

of residual cellulose which distincuy affects the develop ment of severe meteorism at high altitude It would be a mistake to decrease the quantity of fat below the re quired minimum since this would damage the thermal and metabolic balance of the human organism Sweet and sour cream buttered sandwiches and also creamery butter in cooking must be included in flyers food rations Bacon ham and goose should be avoided immediately before and during flights The proteins in the daily rations must not be decreased below the normal minimum Care fully verified studies on vitamin C point to the necessity of increasing its intake in anoxia Therefore fruit juices tomato juice and fresh vegetables should be included in the diet An infusion of sweet briar is recommended as a drink instead of tea or water Campbell s work shows that cell residues seem essential for high flying It would be a mistake to exclude black bread and vegetables from the diet because they contain roughage they should be limited only preceding flight

Dehydration Analysis of Methods Used in Diagnosis S Lloyd Teitelman (M C U S A) states that early recognition and treatment are of the utmost importance Clinical symptoms and signs are characteristic but appear late Measurement of urinary output is not an accurate index of the extent of dehydration Change in hemocon centration is an early and reliable finding as evidenced by increase in the red cell count hemoglobin hematocrit reading blood specific gravity serum and plasma protein concentrations Certain pitfalls must be borne in mind in evaluating these tests Study of the electrolyte pattern of blood plasma is helpful but time consuming and changes are slow to appear Blood volume and available fluid volume determinations are generally not applicable to the study and treatment of early clinical dehydration. The McClure Aldrich test as a means of estimation of the fluid need of the interstitial tissues requires further study

The various methods used in diagnosis of dehydra

(8) Su g Gy ec. & Ob t 78 105 108 F br ry 1944

tion are useful in the rational direction of its treatment

Chloride Excretion Test (Cutler-Wilder Power Test) in Asthenia. Karl E Paschkis and Alison H Price[9] (*Jefferson Med College*) used this test in 50 patients in whom clinical observation failed to reveal any organic disease 27 complained of asthenia and 38 were found to be psychoneurotic Chloride concentration was 125 mg per cent (upper limit of normal according to Cutler *et al*) or above in 13 patients and 225 mg per cent or above in 4 patients not having Addison s disease or any organic disorder

The test was performed two or more times in 12 cases A considerable variability in chloride retaining power was found in 11 even when the test was repeated at short intervals

In five normal subjects chloride excretion showed little variation and no influence of the menstrual cycle

It is concluded that some patients with asthenia and exhaustion may temporarily show signs of adrenal cortical insufficiency Observation of these patients showed that they did not have mild Addison s disease or mild hypoadrenia If their inability to conserve chloride is due to lowering of the function of the adrenal cortex this hypo*function is temporary* It is possible that such fluctuations of adrenal cortical function may be part of a general instability of such personalities

Obesity Challenge to the Psychiatrist. Horace Gray[1] (Stanford Univ) gave 212 obese patients diet lists which provided carbohydrates 80 Gm protein 60 Gm fat 40 Gm yielding 900 calories Considerable time was spent in *trying to stimulate patients interest and to meet their* desires by variations and after the first month by modifications But habits of overeating are seldom reformed except by abrupt renunciation or when the patient s will is inadequate by psychiatric aid

Gray uses the specific sacrifice to enlist the patient s

(9) J Clin I e t gat n 23 29 36 J uary 1944
(1) Stanfo d M. Bull 1 195 1943

co operation This consists of a flour free diet for one month after which 19 of 20 patients will cease to miss foods made of flour and will wish to go on without them Unfortunately 54 per cent of those enlisted in this program fail to see it through for a month

At each visit patients are required to bring a food diary for the day before stating approximate quantities Those who continue to evade bringing a list reveal mental resistances which need mental more than dietary therapy

Belladonna amphetamine and propadrine are of little value Pituitary injections are rarely useful Neutralization of excessive pancreatic secretion by sucrose tablets is occasionally helpful Thyroid by mouth is often useful even when the basal metabolism is within normal limits Low calorie diet still is the accepted sheet anchor

Psychic frustrations with unconscious compensations by nibbling need attention in most cases But satisfaction of the ego by eating and drinking has been neglected

Treatment of obesity depends more on the mind than on the body Many indeed most plump patients need their will supported by insight into their personal problems with their environment To develop such insight is a challenge to psychiatry Three developments are necessary (1) selection by professors of neuropsychiatry from among their interns of those who are temperamentally suited to take up psychotherapy as distinguished from neurologic diagnosis (2) inclusion by psychiatrists of obesity among the problems fit for their art (3) effort by the experts to pause periodically in their insistence on individual investigations in order to consolidate and simplify for the general practitioner all that twentieth century studies of dreams and associations have uncovered about unconscious motives

[Attempt to correct obesity like the cigaret habit or morphinism often prove extremely difficult This is particularly true of the middle aged obese woman who likes to eat or the pampered child even though the need for reduction may be urgent Such reduction can almost invariably be accomplished by an adequate reduction in the caloric intake granting one

gets the complete and sustained co-operation of the patient. We feel that resorting to drugs or other measures is rarely necessary —Ed]

Hyperkinetic Diseases Eli Moschcowitz (Columbia Univ) *presents the concept that certain disease that may* be called hyperkinetic represent primary exaggerations of bodily functions with morbid anatomic changes as a sequel instead of the usually accepted reversed order of disease process *Tentatively* the following diseases are submitted (1) h*ypertension of the greater circulation* which represents an exaggeration of normal intra arterial pressure and leads to arteriosclerosis and the cardiovascular renal syndrome (2) Graves s disease which repre*sents in greater part at least an exaggeration of the nor*mal basal metabolic rate (3) peptic ulcer in which one of the dominant expressions is exaggerated acidity and secretion of the normal stomach (4) cardiospasm which represents an increase in normal tone of the cardiac *sphincter (5) spastic colon and mucous and ulcerative* colitis which represent exaggeration of normal tonicity peristalsis and secretion of mucus of the colon (6) manic depressive psychosis which represents an exaggeration *of a normal rhythm (7) paranoia which represents an* exaggeration of the affective functions

These maladies have certain common denominators The constitution is usually a combination of phenotypic and genetic characters The direct stimuli are malad justments between the psyche and the environment These diseases are essentially limited to the human species and are mostly products of civilization Experimentally they cannot be reproduced in animals except by methods un physiologic for human beings They rarely occur before the emotive faculties are fully developed and possess a remarkable tendency to recur Because transition from normal to abnormal is gradual no specific diagnostic test is *applicable unless it is an arbitrary one* Diagnosis therefore must depend on a study of the composite picture—the organ—personality These diseases as a rule evolve through five stages constitution exaggeration of *function*

(2) Am. J M. Sc. 06 576-598 N ember 1945

lability of signs and symptoms fixation of this exaggeration of function and finally somatic changes

Prevention of Vitamin Deficiencies in Wartime is outlined by Franz R Stenzel (Waban Mass) Deficiency in the A group of vitamins can be avoided by the daily intake of leafy and yellow vegetables and by use of fortified oleomargarine when dairy products are unavailable in adequate amounts Deficiency in the vitamin B group is best controlled by use of fortified bread The physician should encourage use of whole grain bread and cereals The constant use of toasted bread should be discouraged The average adult should drink 1 pt milk daily or its equivalent in the form of evaporated or dried milk used in food Ascorbic acid deficiency can be prevented by increased use of a varied diet containing fruits berries and vegetables Deficiency in the vitamin D group can best be prevented by adequate exposure to sunlight and ingestion of eggs and liver when available If these foods are unavailable irradiation of food may become more widespread Routine use of fish oil concentrates may be advisable under special conditions

Pharmacologic and Clinical Study of Spasmolytic Drugs H Necheles Wm H Olson F Neuwelt and E Spier (Michael Reese Hosp) studied the effects of atropine sulfate papaverine HCl amyl nitrite nitroglycerin trasentin trasentin 6H trasentin A DL 219 (tropic acid diethylaminoethylpropionylbenzylalcohol hydrochloride) and cyverine on salivary gastric and pancreatic secretion and on gastric and intestinal motility of the dog Effects of the drugs on the salivary secretion of the normal human subject and on the resistance of the sphincter of Oddi of patients were determined Finally clinical results of use of trasentin 6H in 38 patients with various gastro-intestinal diseases were observed

Comparison of the value of the different drug on gastro intestinal symptoms showed that atropine and trasentin and in spasm of the sphincter of Oddi trasentin

(3) New Engl d J M d 2 9 859 862 Dec. 1943
(4) Ca t oe terology 2 46 59 J ry 1944

or nitroglycerin were most effective Trasentin yields a smaller incidence of undesirable side reactions than trasentin 6H Syntropan had the least effect on salivary secretion From the clinical study the authors conclude that trasentin 6H is not so useful as trasentin but that they both have important therapeutic aspects

Addisonian Pernicious Anemia without Achlorhydria Does It Exist? John Martin Askey (Univ of Southern California) reviewed 47 reported cases of supposed pernicious anemia without achlorhydria None of these was proved by complete precise criteria to be addisonian pernicious anemia It would seem wise to restrict the term pernicious anemia to the true or addisonian pernicious anemia characterized by absolute anacidity loss of intrinsic factor and reduction of the specific liver principle Until precise critical tests have proved that acid secretion can persist in pernicious anemia presence of acid in any case must be considered as ruling out addisonian pernicious anemia Existence of true pernicious anemia without anacidity cannot yet be accepted

[*No acid no ulcer is a generally accepted medical truism* But with even greater finality we can say "no anacidity no *pernicious anemia.* —Ed.]

Use of Synthetic Diet for Food Allergy and Typhoid William Harwood Olmsted Carl Gayler Harford Stanley Forrest Hampton and Marjorie Jorgenson (Washington Univ) describe a diet composed of amino acids dextrose and emulsified oil to which is added a salt mixture and crystalline vitamins Its use is suggested in food allergy or severe infections of the intestinal tract and as a means of determining the requirements for certain vitamins Experience with this diet in patients with allergy (Table 1) suggests that it is useful for maintaining nutrition fully (Table 2) while determining whether or not a patient is sensitive to food Principles on which use of the diet rests indicate its usefulness for patients with typhoid and other ulcerative lesions of the lower intestinal tract

(5) G t oenter logy 2 1 11 J ary 1944
(6) Arch Int Med 73 341 348 Ap 1 1944

TABLE 1.—DATA FOR ALLERGIC PATIENTS GIVEN SYNTHETIC DIET

Diagnosis, Sex Age (Yr.)	Days on Diet	Method of Admin.	Progress on Diet	Foods as Etiologic Factor
Neurodermatitis F 15	23	Tube	No improvement	None
Eczema F 38	5	Tube	Improvement rapid	Important
Purpura F 51	11	Mouth	Improvement rapid	Important
Bronchial asthma F 20	5	*Mouth*	Improvement	Minor but definite
Colitis (allergic) F 48	2	Tube	Complete relief	Complete
Neurodermatitis F 36	12	Tube	Improvement	Important
Henoch's purpura F 15	14	Tube	Great improvement	Important
Colitis purpura F 35	3	Tube	Complete relief	Complete
Purpura (abdominal pain) F 20	14	Tube	Partial relief	Minor or none

TABLE 2.—CALORIC VALUE OF SYNTHETIC DIET

Calories	24 Hr. Vol. Cc.	Amino-Acids Gm.	Fat Gm.	Dextrose Gm.	Salt Mixture Gm.
1,500	1 080	42	84	150	16
2,000	1 440	56	112	200	16
2,500	1,800	70	140	250	20
3 000	2,160	84	168	300	24
3,500	2 620	98	196	350′	28
4,000	2,880	112	222	400	32

Amigen (Mead Johnson)

Skin Changes of Nutritional Origin are discussed by Harold Jeghers (Boston Univ.) Numerous cases of carotenemia have been reported. Alpha, beta and gamma carotene, cryptoxanthine and *xanthophyll* are the most im portant pigments causing carotenemia in man. Carotenemia usually implies a yellow color of the skin and serum; carotenoderma is a most descriptive term for the skin pig mentation. Carotenemia seems to be harmless even when present for months. Eventually it disappears when caro tene consumption is reduced. Carotenemia is frequent in

(7) N w E gland J M d 2 8 6 8 685 M y 27 714-723 J 3 1943

diabetics and may be present with kidney Simmonds and liver disease The disorder is said to develop more readily in children than in adults Rationing causing increased consumption of fresh vegetables may make carotenemia more prevalent than in the past Yellow pigmentation is noticeable first in the nasolabial folds and on the forehead where sebaceous glands abound and in the palms and soles where the horny layer is thickest When carotenemia is long standing the rest of the skin becomes pigmented Mucous membranes and sclerae are not stained by carotene in contrast to true jaundice but subconjunctival or submucosal fat may be stained and lead to confusion There is no significant change in color of urine or stools The three layer test of Greene and Blackford permits diagnosis of carotenemia even when excess bilirubin is present in the blood

In vitamin A deficiency the early skin change is dryness (xeroderma) When more severe it results in hyperkeratosis follicularis The papular eruption has been called goose skin Phrynoderma (toad skin) is most descriptive of the dermal manifestations of severe avitaminosis A It usually requires two to four months or longer of vigorous treatment The specificity of these lesions rests on their frequent association with xerosis and impaired dark adaptation dietary history of inadequate intake of vitamin A and response to vitamin A therapy In addition they have been produced experimentally in man

Convincing evidence has linked the pathogenesis of keratosis follicularis (Darier s disease) to some abnormality of vitamin A metabolism With massive doses of vitamin A the results have on the whole been favorable the skin usually improved but did not become entirely normal suggesting that there may be other factors in pathogenesis

The essential pathologic process of pityriasis rubra pilaris is follicular hyperkeratosis whose resemblance to the skin lesions of avitaminosis A is noteworthy Brunsting and Sheard demonstrated impaired dark adaptation in three patients Continued vitamin A therapy resulted

in slow and definite but not complete improvement of the skin lesions They consider that in part at least the disease may be due to a disturbed vitamin A metabolism

Various considerations link ichthyosis simplex to vitamin A deficiency Rapaport and co-workers had six patients five with impaired dark adaptation Night blindness responded readily to vitamin A therapy and the skin lesions only after prolonged use of large doses Improvement in the skin was striking but was not complete The hereditary mechanism often present in ichthyosis is explained as possibly one of inheritance of some disorder of vitamin A metabolism Some other nutritional factor may also play an accessory role

Sjogren s syndrome is considered a manifestation of vitamin A deficiency Although the syndrome is not predominantly one of the skin it is mentioned to stress the widening concept of clinical disorders attributable to avitaminosis A Other conditions attributed to vitamin A deficiency are all characterized by abnormalities of keratinization of epithelium of the skin

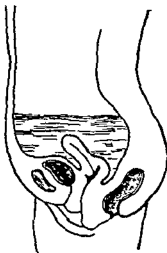
The relation of cheilosis to ariboflavinosis is not as clearcut as originally believed Pyridoxine and pantothenic acid have been suggested as necessary for proper metabolism of riboflavin thus affording a possible explanation of the inconstant response of cheilosis to riboflavin therapy An early lesion of riboflavin deficiency is angular stomatitis of Stannus or Sebrell s lesion It may precede or accompany cheilosis Not all commissural fissures are nutritional a situation more evident in private practice than in the clinic

Deficiencies of vitamins C K and probably P produce a hemorrhagic diathesis Cutaneous purpura may be striking in vitamin K deficiency Ecchymoses and suffusions of blood are common and especially prominent over pressure areas but lack the orthostatic tendency common in scurvy Bleeding may occur from the gums after slight trauma. Bleeding time is usually normal and capillary fragility unaltered Diagnosis depends on decreased pro

of saline were injected until a range of 2 in or more of change by both tests had been obtained

By the standard method the smallest quantity of fluid necessary to effect a 2 in fluctuation was 500 cc and the largest 1 100 cc By the proposed method 200 cc produced a significant change in two subjects 300 cc in three 400 cc in four and 500 cc in one (the most obese subject)

PROCEDURE —The patient empties the bladder at the start of the examination He then lies down and the examiner percusses the midline toward the symphysis pubis until a change in



F g 11 —Flu d le l t se h gh on bd m nal w ll lat ly n ow pel (C urte y of M ses Wm R wo th M J 39 985 987 De mber 1946)

note occurs If there is but little fluid present the symphysis itself is the point of change The patient then stands and bends forward about 10 degrees The level of percussion note change is then compared with that in the supine position

This method owes its superiority to the facts that because of the narrowness of the pelvis a given quantity of fluid will rise higher and be more easily detectable when the patient is erect the problem of percussing the narrow angle between the bed and the belly is circumvented by the standing position and finally the pseudoshift caused by the right and left segments of the colon is ted

Studies on Experimentally Provoked Ileus with Reference to Inhalational Therapy Lars Troell[5] (Karolinska Institutet Stockholm) studied intestinal gas diffusion in rabbits with experimentally induced ileus After injection of 20 cc nitrogen or hydrogen into closed intestinal loops of definite lengths the animals were placed in a 30 L pressure chamber In accordance with a definite scheme for each series of 10 animals they breathed pure oxygen or oxygen mixed with carbon dioxide nitrogen or helium in various concentrations at pressures of 1 and 2 atmospheres At the end of the inhalation therapy the gas remaining in the intestinal loop was measured and its percentage composition determined The average was calculated for each series in order to determine (1) the reduction in total volume of the gas and (2) the reduction of the original quantity of gas injected

Continuous breathing of 100 per cent oxygen at a pressure of 1 atmosphere produced slight to strong inhibition of motility in about 50 per cent of the animals after four to five hours in the other animals there was no motility inhibition Continuous breathing of 100 per cent oxygen at 2 atmospheres pressure produced moderate inhibition in all animals after about three hours and almost complete inhibition after six hours After oxygen inhalation had been concluded normal motility returned after 10 minutes to 2 hours Partial pressure of 4–8 per cent carbon dioxide in the gas inhaled did not hasten the inhibition which made its appearance when 100 per cent oxygen was breathed at 2 atmospheres pressure The experiments indicated that inhibition of motility is a sign of oxygen poisoning

The results of the diffusion and motility tests supported the opinion that prolonged inhalation of 100 per cent oxygen has an unsatisfactory effect on the organism consequently in treatment of ileus inhalation of 100 per cent oxygen should be replaced by inhalation of a mixture of 60 per cent oxygen in helium and of 100 per cent oxygen A small percentage of carbon dioxide does not

(5) Act h Sca d (pp) 95 5 112 1947

increase the toxicity of oxygen at pressures up to 2 atmospheres rather it has a favorable effect on gas diffusion When excess pressure inhalation therapy is used, which also has a favorable effect on gas diffusion 100 per cent oxygen should be used and the time should not exceed two hours

From the clinical standpoint it is important that inhalation treatment of ileus be started early It is desirable that intraduodenal Wangensteen suction be used simultaneously

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NUTRITION

Scorbutic Vertigo On the basis of clinical experience with 87 cases of vertigo associated with scurvy observed between 1929 and 1943 Harald Öhnell[6] (Stockholm) states that there is a probability verging on certitude that vertigo may originate in scurvy Experiments on scorbutic monkeys revealed pathologic anatomic changes in the inner ear which according to generally accepted theories, are significant with regard to the appearance of vertigo Previous etiologic theories for vertigo except that of syphilitic and to some extent that of allergic vertigo offer no possibility for an attack on underlying causes of the disease Scurvy therefore seems to deserve particular attention from diagnostic and therapeutic points of view

Abdominal Nutritional Allergy from Viewpoint of the Surgeon Study of skin tests performed on 750 patients mostly surgical and histologic examinations of surgical specimens of the stomach gallbladder and appendix from the skin tested and other patients led Rolf Kaijser[7] (Univ of Uppsala) to make the following conclusions Food allergy is not a significant factor in the pathogenesis of peptic ulcer but may be present concomitantly with an ulcer Local tissue eosinophilia observed in and near the ulcer is probably due mainly to local changes within the ulcer Exogenous irritations notably those due

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(6) Ga troente logi 71 129 141 1946
(7) Acta ch r Scandin (pp 111) 94 1 337 194

to food allergy also may cause eosinophilia of the gastric mucosa The author describes a few cases of gastritis probably of nutritive allergic origin with marked eosinophilia

Food allergy is not considered to play an important role in the etiology of diseases of the biliary tract although acute biliary colic may be provoked by allergic reactions to food and although certain indefinite abdominal symptoms may remain after cholecystectomy as result of food allergy As compared with a control series the patients with diseases of the gallbladder and bile ducts and patients with gastroduodenal ulcers showed a slightly higher incidence of allergic symptoms However there is no reason to suppose that this was due to a higher incidence of food sensitization The local tissue eosinophilia in the gall bladder noted in some cases is a manifestation either of developing ordinary cholecystitis or of a special type of cholecystitis with a less violent course and possibly an allergic origin Certain circumstances point to the latter interpretation However there is no reason to believe that food allergy has a significant role in the origin of this cholecystitis with local eosinophilia

Food allergy likewise is probably not significant in the etiology of appendicitis The local eosinophilia observed in the mucosa in appendicitis without signs of acute inflammation is most likely related to conditions arising from the lumen of the organ Regarding the eosinophilia which in certain cases of acute appendicitis is present in all layers of the appendical wall the same conclusions apply as to the eosinophilia of cholecystitis Both in diseases of the biliary tract and in appendicitis an increased incidence of allergy as shown by skin tests was found in connection with acute inflammatory diseases This increase was probably due to the rise in general reactivity of the organism usually associated with acute inflammatory conditions

As to the significance of allergy in other less well definable abdominal symptoms the author states that when symptoms characteristic of gastritis enteritis or colitis

prevail, food allergy obviously may be operative but it is not predominant in a larger series of cases Patients with symptoms of enteritis are of special interest to the surgeon for they exhibit the clinical features of an acute abdominal injury The author discusses the clinical picture and diagnosis of acute abdominal conditions due to food allergy

Pathologic anatomic studies led to the conclusion that tissue eosinophilia at the base of a peptic ulcer and in some cases of cholecystitis and appendicitis depends on resorption of certain catabolic products of proteins from the peptic zone or the inflammatory exudate That eosinophilia is usually greatly increased in the presence of allergic reactions may be due to the fact that the developing exudate has a special composition with a pronounced eosinotactic effect which results in early and massive appearance of eosinophilic leukocytes

Hunger Diseases during Period of Famine in 1945 in western Netherlands are described by J Wittop Koning[8] (The Hague) Cachexia is the outstanding physiologic morbid process in chronic hunger the patient dies of exsiccation Phleboclysis with hypertonic (3 per cent) saline may be lifesaving Hunger edema may be caused by endarteritis the symptoms resemble those of thromboangiitis obliterans A number of other symptoms can be easily explained by the assumption that there are vascular disturbances in parts other than the lower extremities These symptoms may retrogress completely

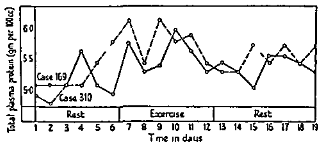
Avitaminoses played an important role Many symptoms of vascular origin disappeared with injections of vitamin B_1 and pellagra like manifestations responded well to nicotinic acid In a number of cases the blood calcium content was considerably reduced

Hunger Edema F A Denz[9] studied a small number of German civilian internees with edema The edema was classified as slight when *confined* to the feet moderate when well developed in the feet and ankles and severe

(8) Gastroenterologia 71 3 338 1946
(9) Quart J Med 16 1 1 January 194

when involving the legs and in a few patients the abdomen and face No case of gross edema was observed

The total plasma proteins were decreased in the persons with edema Mean values of 5 24 Gm per 100 cc plasma in patients with slight edema 5 07 in patients with moderate edema and 4 90 in patients with severe edema were obtained the mean value for a normal control group was 7 04 Gm Plasma albumin values in 14 patients with edema ranged from 2 58 to 3 81 Gm per 100 cc plasma The lowered plasma proteins were believed to result in accumulation of edema fluid commencing with the first



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lowering of the protein level The view that there is a critical level of plasma protein for the production of edema is not accepted

Determinations of plasma volume by the Evans blue method gave values of 1 74–3 30 L per sq M body surface High values were obtained while edema was present and when the examination was repeated after disappearance of edema plasma volume fell to normal This fall in plasma volume was associated with hemoconcentration as shown by rise in hemoglobin and plasma protein levels This fact was taken to indicate that hydremia occurs in hunger edema

In four patients with apparently cured edema exercise caused edema to reappear two patients with edema were

exercised while receiving a full diet and the edema persisted until they were allowed complete rest. Exercise appears to be a potent factor in the production and persistence of edema.

Daily determinations of plasma protein in patients with edema showed diurnal variations (Fig. 113) which were probably due to variations in the degree of hydration of the blood.

The inaccuracy of the clinical assessment of edema is illustrated by a patient showing minimal edema who lost 8.5 L. edema fluid whereas another patient showing severe edema lost only 2 L. edema fluid. Much excess fluid may be hidden in the deeper connective tissues of the mediastinum and abdomen.

Extracellular fluid volumes were determined by the thiocyanate method. In nonedematous persons the extracellular fluid was 20–28 per cent body weight. As the edema disappears the extracellular fluid volume decreases. Urinary chloride excretion was high during loss of edema. While as much as 28 Gm. chloride was being lost daily the kidneys were excreting urine of chloride concentration greater than that of the plasma with resultant fall of plasma chloride concentration. During periods of exercise while edema fluid was collecting the urinary chloride concentration was less than that of the plasma, a fact indicating chloride retention. These changes were believed to result from tubular activity.

Studies in Amino Acid Utilization. Essential Amino Acids as Source of Plasma Protein and Erythrocytes in Hypoproteinemic Rat. E. P. Benditt, E. M. Humphreys, R. L. Straube, R. W. Wissler and C. H. Steffee[1] (Univ. of Chicago) found that protein depleted rats could synthesize new plasma protein and erythrocytes on a diet in which the sole source of amino nitrogen was a mixture of crystalline amino acids. The mixture included tryptophane, lysine, methionine, histidine, threonine, valine, leucine, isoleucine, phenylalanine and arginine in proportions corresponding to those found by chemical analysis of casein.

(1) J. Nutrit. n. 33 85-94, January 1947.

Small amounts of six nonessential amino acids were added to bring the nitrogen level to the equivalent of 9 per cent protein (N $\times$ 6 25) Moreover synthesis occurred to an extent comparable to that produced by a diet con taining casein at an equivalent nitrogen level

With synthetic diets identical to those described but lacking one of the amino acids mentioned other than arginine there was poor consumption of the diet and no significant gain in serum protein just as with a diet com pletely lacking in protein The same was true of erythro cyte production On a synthetic amino acid diet entirely lacking arginine a rat could synthesize proteins and eryth rocytes to an extent equaling that produced by casein or amino acid mixtures at equivalent nitrogen levels and containing all essential amino acids including arginine Furthermore the first mentioned nine amino acids alone could act as a source of nitrogen capable of inducing the formation of serum proteins to an extent comparable to that found with the mixture of 16 amino acids (ration A or synthetic casein) or the natural protein Therefore it can be said that nine amino acids only are indispensable in the hypoproteinemic rat for the construction of serum protein and erythrocytes

Some Physiologic Relationships of Protein Fat Choline Methionine Cystine Nicotinic Acid and Tryp tophane were studied in rats by W D Salmon[2] (Ala bama Polytechnic Inst) He found that the primary deficiency in diets containing 18 per cent or less casein was in labile methyl groups unless supplementary choline or methionine was added The deficiency of labile methyl was aggravated by addition of cystine and fat Supple mentary methionine in the form of the free amino acid was more effective than methionine combined in the casein molecule

The second demonstrable deficiency in low fat diets con taining 18 per cent or less casein was nicotinic acid Tryp tophane or a high level of casein (25 per cent) counter acted the nicotinic acid deficiency A high level of fat (30

(2) J N trition 33 155 168 F bru ry 1947

exercised while receiving a full diet and the edema persisted until they were allowed complete rest Exercise appears to be a potent factor in the production and persistence of edema

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(1) J Nutrition 33 85 94 January 1947

mins increases the efficiency of protein utilization and makes relatively low protein diets adequate for growth Dietary fat also, by decreasing the need for nicotinic acid may indirectly conserve ingested tryptophane and thus increase the efficiency of protein utilization

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per cent) also tended to counteract the nicotinic acid deficiency. This was probably a nicotinic acid sparing effect as the energy metabolism shifted from carbohydrate to fat, a reaction indicating that nicotinic acid like thiamine functions primarily in carbohydrate metabolism.

Only when the deficiencies of labile methyl and nicotinic acid were remedied was a deficiency of cystine (or sulfur amino acid) demonstrable. Methionine corrected both the labile methyl and the sulfur amino acid deficiencies.

The study illustrated the way in which the apparent nutritive value of a protein may be influenced by other dietary components. In the absence of choline from the diet of rats labile methyl groups became the first limiting factor of casein. In rats with a relatively high choline requirement this limitation was disastrous in diets containing 15 per cent or less casein and was significant even at a level of 30 per cent casein, particularly if the diets contained cystine and fat. Nicotinic acid was also of major importance. Need for this substance is maximal when the diet is high in sugar and low in fat. In the absence of adequate nicotinic acid the rat might be able to convert tryptophane to nicotinic acid, but in a low casein diet the tryptophane supply was not adequate for this purpose and for tissue formation at the normal rate. The growth promoting effect of fat in the nicotinic acid free low casein diets, explained on the basis of a nicotinic acid sparing action of fat, was nearly as striking and may be as important nutritionally as the thiamine sparing action of fat. A partial explanation of the anomalous effect of cystine in the low fat low casein diets was now obvious: cystine added to such diets cannot be utilized because of the deficiency of nicotinic acid or tryptophane. But it was not clear why the addition of cystine to the nicotinic acid free low casein low fat diets should be harmful.

Although methionine can be used as the source of labile methyl and tryptophane or casein at high levels as the source of nicotinic acid, the economy of using choline and nicotinic acid is obvious. The presence of these two vita

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